SYNTHESIS OF ORGANIC COMPOUNDS OF ARSENIC:

THE PREPARATION OF ACRIDONE ARSONIC ACIDS.

by

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THESIS

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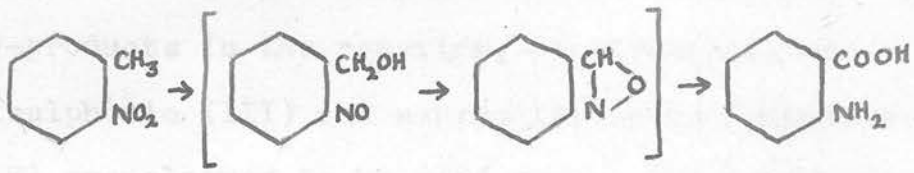
Contents.

EXTENSION OF PREUSS AND BINZ REACTION TO 3 NITRO-4-METHYLPHENYLARSONIC ACID.

Preuss and Binz (Z. ang. Chem., 1900, 16, 385) discovered that o-nitrotoluene on heating with strong sodium hydroxide solution was converted to anthranilic acid. The course of the intramolecular rearrangement was postulated as below.



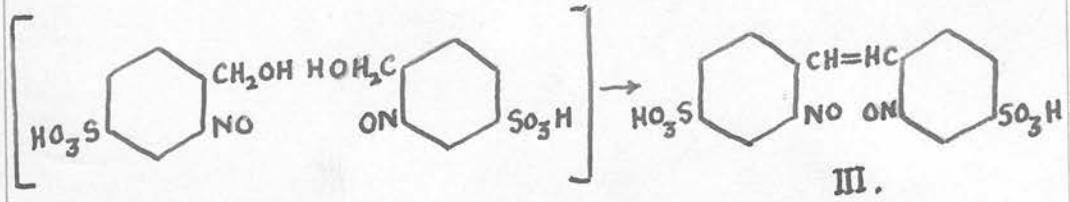
The maximum yield obtained was 20.2%, this resulting from the treatment of two parts of o-nitrotoluene with two parts of sodium hydroxide in one part of water for five hours under reflux. With solid sodium hydroxide the reaction occurred with explosive violence, but on the other hand, no anthranilic acid resulted on treatment with dilute alkali.

In the following year in a patent (D.R.P. 79421: C.1903, I, 371) by Kalle and Company it is claimed that 3-amino-4 carboxyphenylsulphonic acid (I) is obtained/

obtained in good yield by treatment of 3-nitro-4-methylphenylsulphonic acid (II) with 31% sodium

I. II.

hydroxide solution, and this is a suitable method for preparing this compound in the laboratory. As by-products in the reaction, dinitrosostilbene-disulphonic (III) and azoxystilbenedisulphonic acid (IV) are claimed to be produced. The production of these two compounds is evidence for the occurrence of the postulated nitrosobenzyl alcohol and anthranile as successive stages in the original Preuss and Binz reaction with o-nitrotoluene. III May be postulated to result from condensation of two molecules of 2-nitrosobenzyl alcohol-4-sulphonic acid with the loss of two molecules of water. The formation of IV involves a reduction of III with loss of one molecule of oxygen. Thus:



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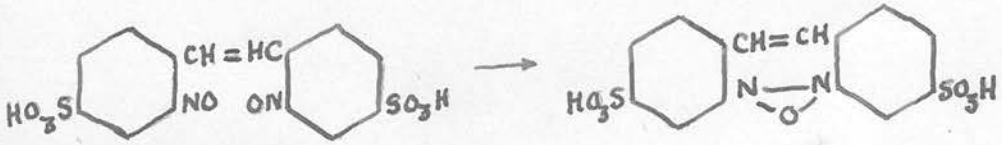


IV.

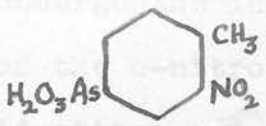
The presence of the sulphonic acid group in o-nitrotoluene appears to facilitate the internal re-arrangement. It therefore appeared of interest to ascertain whether an analogous group such as the arsonic acid group would likewise be favourable to the progress of the reaction. Thus 3-nitro-4-methylphenylarsonic acid (V) would be expected to be converted to 3-amino-4-carboxyphenylarsonic acid (VI).

V. VI.

Apart from the theoretical interest of this reaction, it was desired to prepare a quantity of the expected product (VI) in order to employ it in a series of experiments described in Part III.

At the time when this work was begun, details of the product (VI) had not been published, although it had presumably been prepared about 1915 by Michaelis, as a paper which deals with its therapeutic properties was published after his death/

death, by Sieburg (Z. physiol. Chem. 97, 74: Sitzungsberichte u. Abhandlung der Naturforsch. Ges. zu Rostock. 6, II, 33) who acknowledges receipt of the compound from Michaelis. While the present work was in progress a paper appeared by King, Cohen and Strangeways (J. 1931, II, 3236) in which the preparation and properties of this compound were fully described. These workers prepared the compound by oxidation of 3-nitro-4-methylphenylarsonic acid (V) to 3-nitro-4-carboxyphenylarsonic acid (VII) with alkaline potassium permanganate (Michaelis, Ann. 1902, 320, 321)and subsequent reduction with ferrous chloride and ammonia to the amino acid (VI), which was isolated by making use of its low solubility in water at its isoelectric point.



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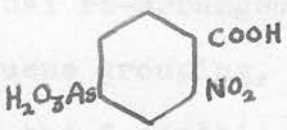


VII.

VI

In the present work, 3-nitro-4-methylphenylarsonic acid was prepared by a Bart reaction on p-toluidine (Bart, Ann. 1922, 429, 74) and a subsequent nitration with a mixture of fuming nitric acid/

acid and concentrated sulphuric acid between 15-25°C. (Michaelis, Ann. 1902, 320, 321) . As Michaelis had been unable to prove the position of the nitro group and had by analogy with the nitration of p-tolylphosphinic acid, assumed it occupied the 3-position, it seemed desirable to synthesise the 3-nitro-4-methylphenylarsonic acid directly by a Bart reaction on o-nitro-p-toluidine. An acid was obtained (in much poorer yield than by the previous method) which in crystalline form and properties, corresponded with the acid previously prepared. This 3-nitro-4-methylphenylarsonic acid and that prepared according to Michaelis could not be identified by the method of mixed melting points, as neither compound melted below 400°C. Both acids undergo the internal re-arrangement characteristic of the o-nitrotoluene grouping, evidence for their identity, and for the 3 position of the nitro group in the acid prepared by the first method.

3-Nitro-4-methylphenylarsonic acid (V) was, in this present work, boiled with various concentrations of aqueous sodium hydroxide solution, and it was found by means of diazotisation of the acidified reaction mixture with sodium nitrite solution/

solution, and subsequent coupling with β-naphthol, that an amino group had been formed in all concentrations from 10% to 45%. A drop of the reaction mixture diluted in water showed a powerful blue-violet fluorescence in arc-light, a property which the nitromethylphenylarsonic acid did not show, but which proved to be characteristic of the desired acid when it was prepared pure by the method of King and co-workers (loc. cit.). Treatment with 30% sodium hydroxide solution gave the maximum yield 15.4% of 3-amino-4-carboxyphenylarsonic acid which was separated from the reaction mixture by dilution, filtration and precipitation with acetic acid at congo purple. The acid was purified by solution in sodium carbonate solution, treatment of the heated solution with charcoal, filtration, and precipitation as previously with acetic acid.

This compound was also prepared by the method of King, Cohen and Strangeways. The properties of the two compounds were carefully compared. Neither melted below 400°C., so that the method of mixed melting points could not be used for identification. The solutions of both compounds in water showed a blue-violet fluorescence dischargable by excess acid or alkali. The precipitated/

precipitated acid was buff in colour in both cases, although on slow separation the acid from the sodium hydroxide reaction produced red prisms which ~~when~~ powdered to form the same buff coloured substance as obtained by rapid precipitation. It would seem that the presence of the arsonic acid group in the molecule favours the internal re-arrangement in the same way as the sulphonic acid group, although to a lesser degree as the yields are lower. It may be noted (cf. experimental section) that a considerable quantity of dark coloured tarry by-products are formed. These may in part consist of compounds analogous to compounds III and IV said to have been isolated when 3-nitro-4-methylphenyl-sulphonic acid is treated with 30% sodium hydroxide solution, but so far no compound other than the 3-amino-4-carboxyphenylarsonic acid has been isolated. Attempts to utilise this acid in the production of acridone-arsonic acids are described in a later section.

EXPERIMENTAL.

p-Tolylarsonic acid (Bart, Ann. 1922, 429, 74).

To 10.7 gm. p-toluidine in 100 c.c. water were added 35 c.c. conc. HCl (8 N.) and after cooling the solution in ice to below 5°C., 6.9 gm. $NaNO_2$ dissolved in 100 c.c. water were introduced with continuous stirring by means of a dropping funnel. A solution of 20 gm. sodium arsenite in 100 c.c. water was added rapidly with efficient stirring to the diazo solution. The mixture was left to stand overnight and to come slowly up to room temperature when nitrogen was evolved. 25 c.c. 5N. NaOH solution was then added until a drop of the solution no longer gave a red coloration with alkaline β-naphthol. Nitrogen was again evolved, the solution was filtered to remove tarry material and concentrated on the water-bath to 200 c.c. Dilute HCl was added until the solution was neutral to litmus, and charcoal was added to the heated solution. After filtering the pale yellow, hot solution was made acid to congo-red with HCl, and allowed to cool. p-Tolylarsonic acid separated out/

out as white needles which were filtered and dried (11.6 gm.).

p-Nitrotolylarsonic acid (Michaelis, Ann. 1902, 320, 321.

11.5 Gm. p-tolylarsonic acid were added in small portions with constant stirring to a mixture of 48 gm. fuming HNO_3 and 31.5 c.c. H_2SO_4 (D. 1.34), the temperature being kept between 15-25°C. The yellow solution resulting was poured into six. times its volume of cold water, from which in a short time the p-nitrotolylarsonic acid separated out as clusters of silky white needles. The acid was purified by washing with cold water, and recrystallisation from boiling water yield 9.1 gm. (79%).

Bart reaction on o-nitro-p-toluidine.

This acid was also prepared directly by a Bart reaction on o-nitro-p-toluidine. 15.2 Gm. o-nitro-p-toluidine dissolved in a mixture of 500 c.c. water and 100 c.c. conc. HCl (8 N), was diazotised below 5°C. with a solution of 8.3 gm. $NaNO_2$ in 100 c.c. water and the diazo solution carefully neutralised to congo red below 0°C. with N. NaOH solution. A solution of 20 gm. sodium arsenite in/

in 200 c.c. water was added rapidly with vigorous stirring, when a violent evolution of N_2 occurred. After this evolution had moderated, the mixture was made alkaline with N. NaOH solution, left to stand overnight, filtered from resinous material, and concentrated on the water-bath to 200 c.c. The concentrate was made weakly acid (congo paper still red), boiled up with charcoal and filtered. The filtrate was made acid to congo red with HCl, and allowed to cool. The arsonic acid separated as yellowish-white needles. Yield 7.4 gm.

This last method gave poorer yields than the previous two-stage method, a larger quantity of tarry material being produced in the Bart reaction on the o-nitro compound than in the case of the p-toluidine itself.

3-Nitro-4-carboxyphenylarsonic acid (Michaelis, Ann. 1902, 320, 321.)

5 Gm. 3-nitro-4-methylphenylarsonic acid and 5 gm. KOH dissolved in 125 c.c. water were added slowly to a solution of 5 gm. $KMnO_4$ in 375 c.c. water at a temperature of 65-70°C. After 5 hours heating, the excess $KMnO_4$ is destroyed by the addition of alcohol, the mixture filtered, the filtrate/

filtrate acidified with HCl, evaporated to dryness, and extracted with alcohol (300 c.c.). By evaporation of the alcohol extract, the acid is obtained in the form of white warty crystals which are pure enough for proceeding to the reduction, although they still contain traces of inorganic salts. Yield 3.9 gm. (79%).

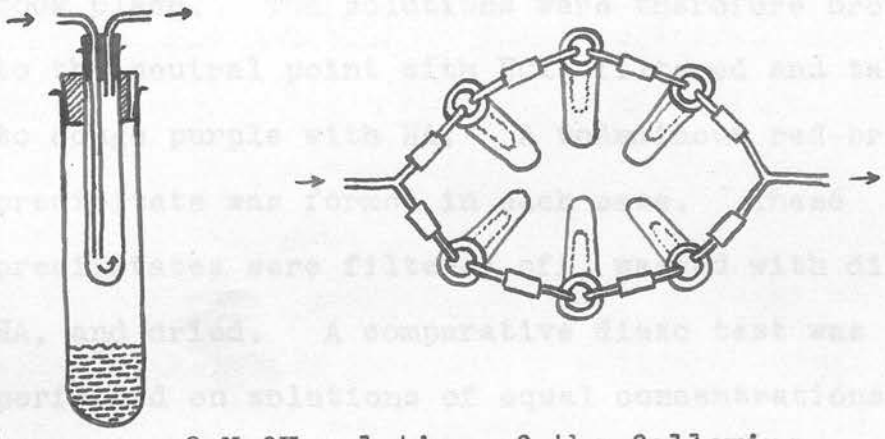
3-amino-4-carboxyphenylarsonic acid (King, Cohen and Strangeways, J. 1931, 3250).

To a solution of 3-nitro-4-carboxyphenyl arsonic acid (22 gm.) in 220 c.c. 2N. NaOH solution at 0°C. were added with vigorous stirring 73 gm. of $FeCl_2$ (10% excess) in 100 c.c. water, and finally 250 c.c. 2N. NaOH solution, the temperature being kept below 0°C. (cf. King and Murch, J. 1924, 2605). The ferric hydroxide was filtered off, and extracted twice with 250 c.c. 0.4N. NaOH solution. The combined filtrates made neutral to congo red, deposited the amino acid, along with partly reduced products. The amino acid was extracteddwith N. HCl until no diazotisable material was left, and precipitated after concentration on the water-bath, by just removing the acidity to congo red with saturated/

saturated sodium acetate solution. The acid separated as a buff coloured precipitate of warty crystals. Yield 6 gm.

3-Amino-4-carboxyphenylarsonic acid.

3-~~Amino~~ Nitro-4-methylphenylarsonic acid (1 gm.) was put in each of six long"boiling tubes" fitted with an internal reflux condenser as shown in the diagram, and heated in an oil-bath. By the use of this form of apparatus, it was possible to get the six tubes compactly into a moderately small oil-bath and thus ensure approximately uniform conditions.



Five c.c. of NaOH solution of the following concentrations were added: 5%, 10%, 15%, 20%, 30%, 45%. In the first four tubes complete solution of the acid in the form of the sodium salt occurred on heating, but in the last two tubes (30% and 45%) some/

some of the solid sodium salt remained undissolved. On continued heating the 5% solution alone remained clear, the others becoming tarred. The gentle boiling was continued for 5-6 hours.

On diazotising and coupling with sodium β-naphtholate, small test portions from each tube, it was then found that in concentrations 10%-45% an amino compound had been formed. To the solutions of concentrations 10%-45% diluted to 10 c.c., 10 c.c. of absolute alcohol was added to precipitate if possible the sodium salt of the acid, and at the same time dissolve up the tar. No precipitation took place. The solutions were therefore brought to the neutral point with HCl, filtered and taken to congo purple with HA. A voluminous red-brown precipitate was formed in each case. These precipitates were filtered off, washed with dilute HA, and dried. A comparative diazo test was performed on solutions of equal concentrations of this crude product. The strongest diazo reaction was given by the product from the 30% NaOH solution, which also showed the most powerful fluorescence when/

when a dilute solution in alkali was transilluminated by arc light.

A second large scale experiment was performed with 13 gm. 3-nitro-4-methylphenylarsonic acid dissolved in 65 c.c. 30% NaOH solution. The dark brown solution resulting after nine hours boiling was neutralised to litmus with HCl, filtered, brought to the neutral point of congo red with dilute HA, and left to stand overnight. A reddish-brown precipitate was formed, was filtered off, dried, and weighed. (6.9 gm.). When dissolved in dilute HCl and treated with $NaNO_2$ with subsequent coupling with sodium β-naphtholate, this precipitate showed a marked diazo reaction. On dissolving in aqueous Na_2CO_3, the solution showed the blue-violet fluorescence characteristic of the 3-amino-4-carboxyphenylarsonic acid.

A further quantity of tarry material whose alkaline solution gave only a very weak diazo reaction, and fluoresced weakly, was obtained by making the filtrate of the reaction mixture acid to congo-red with dilute HCl. No definite compound could be isolated from this material.

The precipitated 3-aminocarboxyphenylarsonic acid/

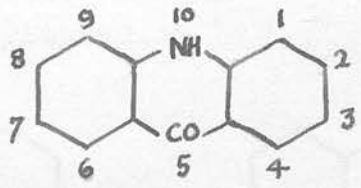
acid was redissolved in Na_2CO_3 solution heated with animal charcoal, filtered, made neutral to litmus with HCl and neutral to congo-red with dilute acetic acid. On standing overnight, red, warty, prisms deposited, were filtered and dried. (3.1 gm.), no m.p. below 400°C. (Found As 29%: $C_7H_8O_5NAs$ requires As 28.7%).

II. /

II. SYNTHESIS OF NITRO- AND AMINOACRIDONES.

For the preparation of acridone-arsonic acids, it was found (cf. Part III) that the only successful method was the synthesis of aminoacridones and their conversion by the Bart reaction into the desired acids.

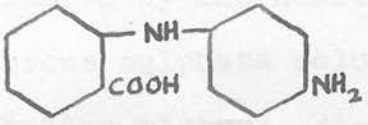
Before proceeding to the description of the literature and work on these substituted acridones it is necessary to state definitely the system used in the numbering of the acridone molecule, as there is at present divergence between the Continental and English methods.



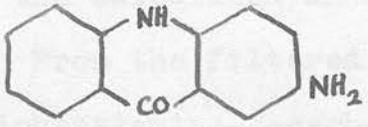
It was found that three of the possible four monoaminoacridones, i.e. 1-, 3-, and 4-amino-acridones had been synthesised by Ullmann and Bader (Ann. 355, 312). Of these three, 1-aminoacridone was of no use for this work, as according to Clemo, Perkin and Robinson (J. 1924, 1751) on diazotisation it/

it was converted into the triazole derivative, so presumably no substitution of the diazonium chloride group by the arsonic acid group was then possible.

It was therefore decided to prepare 3-amino-acridone. The synthesis according to Ullmann and Bader was repeated. o-Bromobenzoic acid was condensed with p-phenylenediamine in amyl alcohol solution in the presence of potassium carbonate and copper catalyst to form 4'-aminophenylamine-2-carboxylic acid (VIII) which was cyclised in solution in 96% sulphuric acid at 100° to form 3-aminoacridone (IX). The aminoacridone was isolated by pouring the sulphuric acid solution into water and making the solution alkaline with sodium carbonate, when the base was precipitated.



VIII.



IX.

This process gave poor yields on the large scale, owing to the ease of oxidation of both the diamine and aminoacid at the temperature (145-150°) of the condensation/

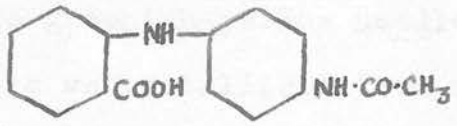
condensation reaction.

A method of synthesis giving improved yields was worked out as follows. Anthranilic acid was condensed with p-nitrochlorobenzene in presence of potassium carbonate and copper catalyst at 220° (cf. Clemo, Perkin, and Robinson, J. 1924, 1751). The resulting melt of potassium 4'-nitrodiphenylamine-2-carboxylate was dissolved in water and the excess nitrochlorobenzene removed in a current of steam. The green 4'-nitrodiphenylamine-2-carboxylic acid (cf. Goldberg Ber. 39, 1691) obtained by acidification of the alkaline solution, was obtained in 95% yield, and after one recrystallisation from xylene was pure enough for use in the next stage in the synthesis.

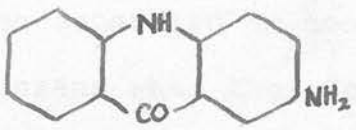
The acid was reduced at 70° in excess ammonia solution by the addition of the calculated amount of ferrous sulphate solution. From the filtered reaction mixture, 4'-aminodiphenylamine-2-carboxylic acid was precipitated at its iso-electric point by the addition of dilute hydrochloric acid. The bluish-white acid was dried to constant weight (80% yield) in a vacuum desiccator. By the avoidance of the use of heat in the drying, very little oxidation of the amino acid occurred. Care had nevertheless to be taken that the acid was left for the shortest possible/

possible time in ammoniacal solution, as the ammonium salt was easily oxidisable in the dissolved state.

A further improvement in the method of synthesis and in the magnitude of the yields, was effected by condensing o-bromo-benzoic acid with p-aminoacetanilide in amyl alcohol solution in the presence of potassium carbonate and copper catalyst, to form 4'-acetamidodiphenylamine-2-carboxylic acid (X) in 88% yield. The methyl ester of this compound had been prepared by Goldstein and Rodel (Helv. Chim. Act. 9, 765) but the acid itself had not been isolated.



X.

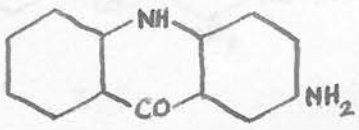


IX.

By treatment of this acid with 96% sulphuric acid at 100°, and subsequent boiling for one hour after dilution to 50% sulphuric acid, 3-aminoacridone was obtained in 90% yield after isolation in the manner previously described. In the one process, condensation to the acridone and hydrolysis of the acetamido group had been accomplished.

The 3-aminoacridone was recrystallised from alcohol/

alcohol, being then pure enough for use. m.p. 295° (Ullmann and Bader, pure m.p. 298°).



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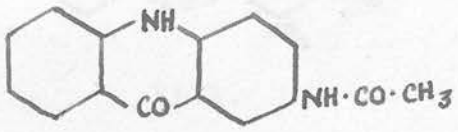
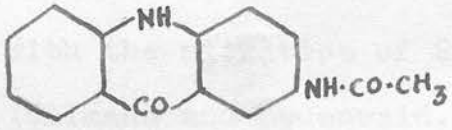


XI.

This compound was converted to 3-acetamido-acridone (XI)(cf. Goldstein and Rodel, Helv. Chim. Act. 9, 765) by solution in glacial acetic acid and addition of the calculated amount of acetic anhydride. The greenish-yellow needles which separated on cooling, were recrystallised from nitrobenzene when they formed grayish-white clusters of needles, m.p. 397°. (Goldstein and Rodel give no m.p. below 330°).



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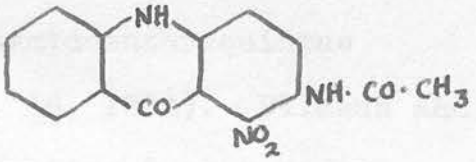
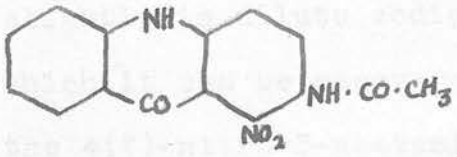


XII.

3-Acetaminoacridone was nitrated in sulphuric acid solution below 0°, by a mixture of concentrated nitric and sulphuric acids. On pouring into water, a brown mass was formed which on being recrystallised from glacial acetic acid, yielded orange needles of(?)nitro-

3-/

3-acetamidoacridone (XII), no m.p. below 400°C.



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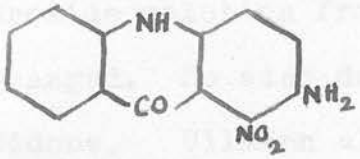
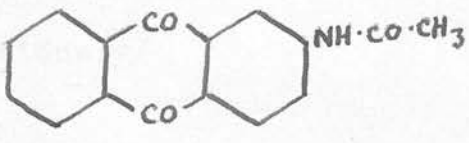
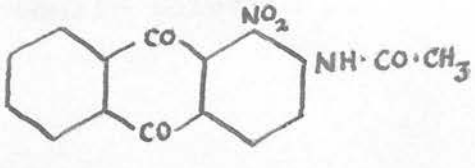


XIII.

This compound was hydrolysed in 50% sulphuric acid at 100° to yield the deep red nitroaminoacridone. The (?)nitro-3-aminoacridone (XIII) formed a yellow sulphate, and recrystallised from nitrobenzene in crimson needles, no m.p. below 400°.

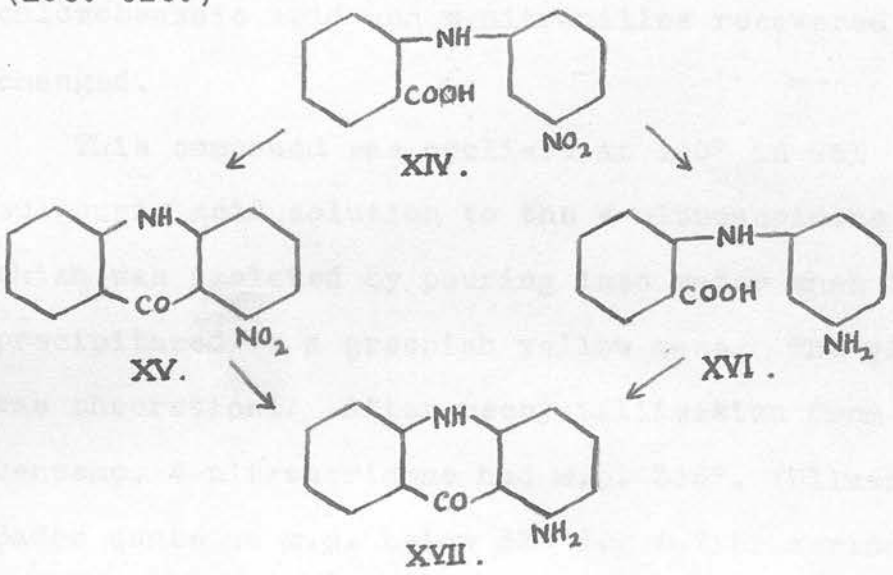
On general grounds it would be expected that the nitro group would enter into the o-position to the acetamido group, the p-position being blocked, thus forming either the 3-acetamido-4-nitro, or 2-nitro-3-acetamidoacridone. Of these two possibilities the first would seem to be the most probable by analogy with the nitration of 2-acetamidoanthraquinone (Ullmann and Medenwald. Ber. 46, 1804). Ullmann and Medenwald record that on nitrating 2-acetamido-anthraquinone, the chief product was 1-nitro-2-acetamidoanthraquinone, only traces of the isomeric 3-nitro-2-acetamidoanthraquinone being formed at the same time.





The 1-nitro-2-acetamidoanthraquinone dissolves slightly in dilute sodium hydroxide solution from which it can be recovered unchanged. So also does the 4(?)-nitro-3-acetamidoacridone. Ullmann also notes that 2-nitro-acridone dissolves in alcoholic potassium hydroxide solution to form a deep wine-red solution, whereas the 4-nitroacridone forms a reddish-orange solution. 4(?)-nitro-3-acetamidoacridone dissolves to form an orange solution.

4-Aminoacridone was synthesised in the two different methods described by Ullmann and Bader (loc. cit.)



3'-Nitrodiphenylamine-2-carboxylic acid (XIV) was prepared by the condensation of o-chlorobenzoic acid and m-nitraniline in amyl alcoholic solution as previously/

previously described. After the amyl alcohol had been distilled off in a current of steam, the solution of the potassium salt was allowed to cool, and the excess m-nitraniline filtered off. The filtrate was acidified and the greenish-yellow mass of the nitrodiphenylamine acid boiled with hot water to remove excess o-chlorobenzoic acid, dried and washed with benzene. In this way a product was obtained of m.p. 212° (Ullmann and Bader, pure m.p. 218°) pure enough for use in the later stages of the synthesis. Ullmann quotes a maximum yield of 66% In this work a yield of 89% was obtained after due allowance had been made for the quantities of o-chlorobenzoic acid and m-nitraniline recovered unchanged.

This compound was cyclised at 100° in 96% sulphuric acid solution to the 4-nitroacridone (XV) which was isolated by pouring into water when it was precipitated as a greenish yellow mass. The yield was theoretical. After recrystallisation from nitrobenzene, 4-nitroacridone had m.p. 336°. (Ullmann and Bader quote no m.p. below 330°). 4-Nitroacridone dissolved in alcoholic potassium hydroxide solution to form a reddish-orange solution.

The nitroacridone was reduced in alcoholic suspension/

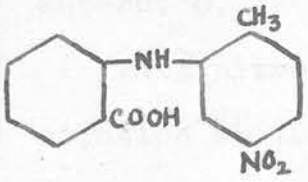
suspension by means of stannous chloride and hydrochloric acid. The compound dissolved up on heating under reflux on the water bath and at the same time fluorescence developed in the solution. The orange tin salt was precipitated by the addition of dilute aqueous ammonia, and redissolved in aqueous alcoholic hydrochloric acid. Sulphuretted hydrogen was passed into the solution heated to 70°, when the tin was precipitated as the sulphide. After filtration the solution was made alkaline with ammonia and the precipitated yellow 4-aminoacridone (XVII) filtered off, dried and recrystallised from aqueous alcohol. The yield by this method was poor.

3'-Nitrodiphenylamine-2-carboxylic acid (XIV) was reduced at 70° in excess ammonia solution and the resulting 3'-aminodiphenylamine-2-carboxylic acid (XVI) isolated in the same manner as the 4'-amino isomer. The grayish-white acid (95% yield) had m.p. 164° (Ullmann and Bader pure m.p. 166°) and was pure enough for conversion to the acridone.

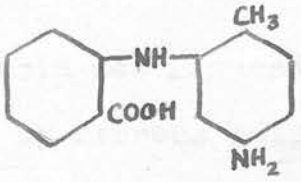
The amino acid was cyclised at 100° in 96% sulphuric acid solution and the 4-aminoacridone (82% yield) isolated in the same manner as the 3-aminoacridone. The compound after recrystallisation

from/

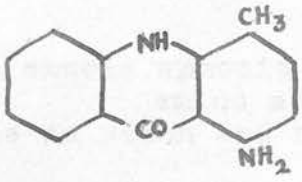
from aqueous alcohol, had m.p. 290-291° (Ullmann and Bader give m.p. 285°). A mixed m.p. with the 4-aminoacridone, m.p. 289-290° prepared by reduction of the nitroacridone gave m.p. 289-290°. Both compounds formed a yellow solution in absolute alcohol, developing an intense green fluorescence on the addition of hydrochloric acid, and seemed to be identical in all respects. The cyclisations appear to proceed therefore in the manner stated by Ullmann and Bader.



XVIII



XIX



XX

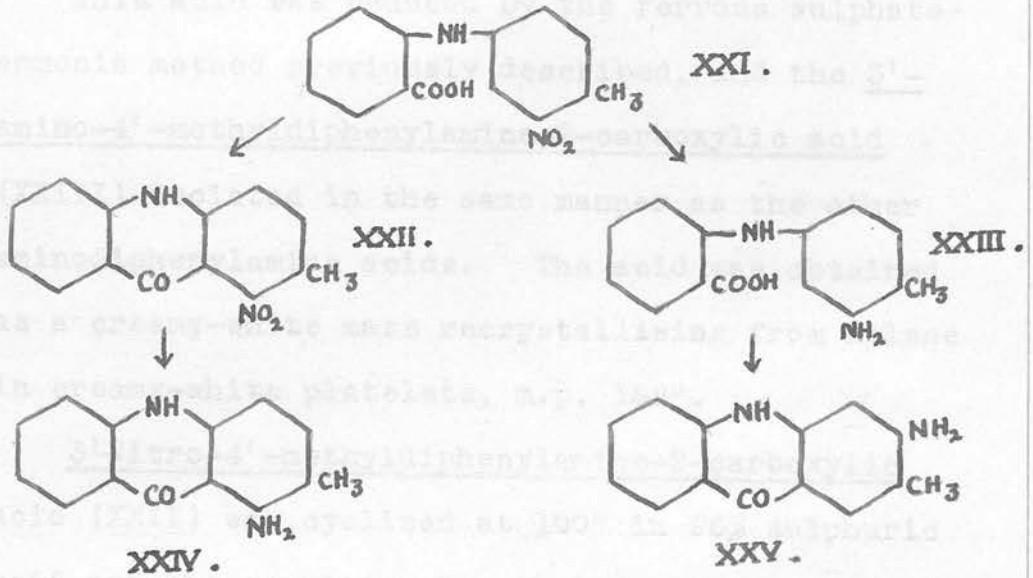
2'-Methyl-5'-nitrodiphenylamine-2-carboxylic acid (XVIII) had been prepared by Clemo, Perkin and Robinson (J. 1924, 1751) but had not been isolated pure, nor had any analysis or m.p. determinations been carried out. The work of these authors was repeated, o-chlorobenzoic acid being condensed with p-/

p-nitro-o-toluidine (4-nitrotolyl-2-amine) in amyl alcohol in the usual manner. The very tarry dark brown product was purified by solution in potassium carbonate solution, and "salting out" by the addition of excess solid potassium carbonate. The potassium salt separated out in crimson rectangular needles. These were redissolved in water, and the solution acidified precipitating the 2'-methyl-5'-nitrodiphenylamine-carboxylic acid (XVIII) as an orange precipitate. After recrystallisation from xylene, the acid formed orange red needles, m.p. 206-207°C.

This nitro acid was reduced in excess ammonia solution at 70° by ferrous sulphate solution and the amino acid isolated in the manner previously described for 4'-amino- and 3'-amino-diphenylamine carboxylic acids. The 2'-methyl-5'-aminodiphenylamine carboxylic acid (XIX) formed brownish-white platelets, m.p. 190°.

This acid was cyclised in 96% sulphuric acid and the 1-methyl-4-aminoacridone formed brown needles m.p. 231°, dissolving in alcohol to give a yellow solution in which a fluorescence did not develop on addition of hydrochloric acid. It was slightly soluble in dilute sodium hydroxide solution, forming a yellow solution. The solution of its diazo/

diazo compound in hydrochloric acid was orange in colour, and coupled with sodium β-naphtholate to give a purple precipitate, the diazo reaction being weak.



3'-Nitro-4'-methyldiphenylamine-2-carboxylic acid (XXI) was prepared by condensation of o-chlorobenzoic acid and o-nitro-p-toluidine (2-nitrotolyl-4-amine) in presence of dry potassium carbonate and copper catalyst at 200-220° for four hours. On addition of water to the dark red melt, heating and allowing to cool, rectangular plates of the crimson potassium salt separated out. By the addition of a large quantity of potassium carbonate, the acid was almost completely precipitated as the potassium salt. The salt was redissolved, the solution acidified, and the 3'-nitro-4'-methyldiphenylamine-2-/

2-carboxylic acid (XXI) obtained as a brown mass which, thrice recrystallised from xylene, formed yellow needles, m.p. 194°.

This acid was reduced by the ferrous sulphate-ammonia method previously described, and the 3'-amino-4'-methyldiphenylamine-2-carboxylic acid (XXIII) isolated in the same manner as the other aminodiphenylamine acids. The acid was obtained as a creamy-white mass recrystallising from xylene in creamy-white platelets, m.p. 188°.

3'-Nitro-4'-methyldiphenylamine-2-carboxylic acid (XXII) was cyclised at 100° in 96% sulphuric acid and the resulting 3-methyl-4-nitroacridone (XXIV) isolated in the same manner as the 4-nitro-acridone. The compound recrystallised from nitro-benzene in clusters of light yellow needles, m.p. 330-331° (decomposition), and dissolved in alcoholic potassium hydroxide solution to give an orange-red solution. Ullmann states that 2-nitroacridone gives a deep wine-red colour in alcoholic potassium hydroxide solution. It was possible that this methylnitroacridone might have been the 2-nitro-3-methylacridone, as cyclisation can take place theoretically to form either the 2- or 4-nitro derivative. The unsubstituted 3'-nitrodiphenyl-amine/

amine-2-carboxylic acid cyclises to form the 4-nitro-acridone, the 2-nitroacridone being prepared by a different method of ring closure from 3-nitrodi-phenylamine-2-carboxylic acid (Ullmann loc.cit.). Owing to the similarity between the reactions of 4-nitro-acridone and the supposed 3-methyl-4-nitro-acridone (XXII) with alcoholic potassium hydroxide solution, and the dissimilarity in the reactions of the 2-nitroacridone and XXII, as well as the evidence furnished by analogy with the cyclisation of the un-substituted nitrodiphenylamine carboxylic acid, it has been assumed that in this paper ~~that~~ XXII is indeed 3-methyl-4-nitroacridone. Further proof is yielded later in the comparison of the properties of the reduction product of this compound (XXII) and 1-methyl-4-aminoacridone (XX).

3-Methyl-4-nitroacridone (XXII) was reduced in alcoholic suspension by means of stannous chloride and hydrochloric acid, and the resulting (?)-amino-3-methylacridone isolated in the same manner as employed for 4-aminoacridone (XVII). The compound was purified according to Ullmann's method by solution in acetic acid and reprecipitation with ammonia, when it formed a bright greenish-yellow powder, m.p. 250° showing a tendency to change on heating/

heating to a bright green colour. It formed a yellow solution in alcohol, becoming pale yellow on the addition of hydrochloric acid. The solution of the diazo compound was orange, and coupled weakly with sodium β-naphtholate to form a reddish-brown insoluble compound. The solution in dilute sodium hydroxide was yellow, and non-fluorescent. In all its reactions, the aminoacridone was very similar to 1-methyl-4-aminoacridone (XX). It has therefore been assumed on the strength of the above evidence that XXIV is 3-methyl-4-aminoacridone.

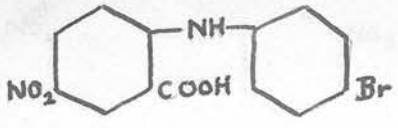
3'-Amino-4'-methyldiphenylamine-2-carboxylic acid (XXIII) was cyclised in 96% sulphuric acid in the usual manner, and the resulting (?) amino-3-methyl-acridone isolated as previously described for 3- and 4-aminoacridones. The compound formed a canary yellow sulphate and recrystallised from aqueous alcohol in greenish-white clusters of needles, m.p. 320°. A mixed m.p. with the 3-methyl-4-amino-acridone gave m.p. 235-240°. The aminoacridone dissolved in alcohol to form a pale yellow solution with a weak purple fluorescence, a brilliant green fluorescence being produced on the addition of hydro-chloric acid. The solution of the diazo compound was/

was deep red and coupled well with sodium β-naphtholate solution to give an insoluble crimson compound. The solution of the compound in dilute sodium hydroxide solution was pale yellow, fluorescing blue.

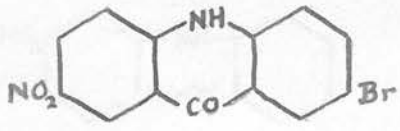
As 2-aminoacridone has apparently never been prepared although as mentioned the 2-nitro-compound is known, no direct comparison with the supposed 2-amino-3-methylacridone (XXV) was possible. It has been assumed therefore that as the balance of evidence is in favour of the view that the orientation of XXIV and XXV is, as stated above, XXV is indeed 2-amino-3-methylacridone. This compound is then the first 2-aminoacridone to have been prepared.

4-Nitro-4'-bromodiphenylamine-2-carboxylic acid (XXVI) (cf. Papasogli, Atti. R. Accad. dei Lincei [5], 33, II, 106) was prepared by condensing 2-bromo-5-nitrobenzoic acid with p-bromoaniline in the usual manner, and the resulting acid obtained as orange platelets of the potassium salt from the solution after steam distillation. By redissolving the potassium salt in water, and acidifying, the acid was obtained as a dark green mass recrystallising from glacial acetic acid as dark green needles, m.p. 284°. Cyclisation to the acridone did not take place in 96% sulphuric acid at 100°, the acid being recovered/

recovered unchanged on dilution. A modification of the Friedel-Craft reaction employed by Ullmann and Bader in the synthesis of 2-nitroacridone was used. The acid was dissolved in nitrobenzene and a slight excess over the calculated amount of phosphorus pentachloride required to convert the acid to the acid chloride, was added and the mixture heated gently until no more fumes of hydrochloric acid gas were liberated. After cooling aluminium chloride was added and the heating continued until again no more fumes of hydrochloric acid gas were liberated. After cooling, the solution was poured on to ice when the 7-nitro-3-bromoacridone (XXVII) partly separated from the nitrobenzene as a brown mass. The nitrobenzene was distilled off from the mixture in a current of steam, and the nitrobromoacridone isolated, and recrystallised from nitrobenzene forming greenish-yellow needles with no m.p. below 400°.



XXVI.



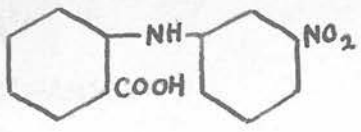
XXVII.

Papasogli claims to have prepared the 4-nitro-4'-bromo/

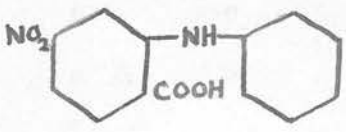
bromodiphenylamine-2-carboxylic acid and 7-nitro-3-bromoacridone but gives no m.pts. and furnishes no analytical figures. He does not describe the preparation of the nitrobromoacridone and describes the diphenylamine acid as forming orange platelets. It would seem probable that this author was working with the potassium salt of the diphenylamine acid.

Cyclisation of substituted Diphenylamine-2-carboxylic Acids.

In the course of this work it seemed advisable to collect and review as much evidence as possible, in regard to the effect of the nature and position of substituents on the cyclisation of diphenylamine-2-carboxylic acids. Lehmstedt (Ber. 1932, 999) had noted that 3'-nitrodiphenylamine-2-carboxylic acid (XXVIII) condensed in concentrated sulphuric acid but that 5-nitrodiphenylamine-2-carboxylic acid (XXIX) did not.



XXVIII.



XXIX.

In the course of the present work, a series of 4-nitro diphenylamine-2-carboxylic acids was prepared by the normal/

normal methods, and attempts made to cyclise them in solution in concentrated sulphuric acid at 100°. In every case, the acid was recovered unchanged.

In the following table those compounds underlined have been prepared for the first time in this research.

Compounds cyclising in sulphuric acid.

(1) 2'-Methyldiphenylamine-2-carboxylic acid.
" 3'- " " " " "
" 4'- " " " " "
" 2'-Chloro " " " "
" 3' " " " " "
" 4' " " " " "
" 4'-Bromo " " " "
" 2'-Methoxy " " " "
(2) 4'- " " " " "
(1) 4'-Ethoxy " " " " (a)
" 5-Methoxy " " " "
" 2'-Carboxy " " " "
" 4' " " " " "
" 3'-Amino " " " "
" 4'- " " " " "
(3) 4'-Acetamido " " " "
(4) 4'-Dimethylamido " " "
(1) 2'-Nitro " " " "
" 3' " " " " "
" 2':4'-Dimethyl " " " "

(5)/

(5) 2'-Methyl-5'-chloro-2-carboxylic acid.

(3) 2'-Methyl-5'-amino " " "

" 2'-Methyl-5-'-nitro " " "

" 4'-Methyl-3'-amino " " "

" 4'-Methyl-3'-nitro " " "

(1) 2':4'-Dichlorodiphenylamine-2-carboxylic acid.

(5) 2':5' " " " "

" 2':5' Dibromo " " "

" 2'-Chloro-5'-nitro " " "

" 2'-Bromo-5'-nitro " " "

" 5'-Chloro-2'-nitro " " "

(6) 2:4-Dinitro " " " (b)

(7) 4:4'-Dinitro " " "

(8) 2'-Carboxy-5'-sulphonic " "

(9) N-Acetic " " "

(10) N-(2-tolyl)-2'-methyl " "

" N-(2-tolyl)- " "

Compounds only cyclising with PCl_5 and $AlCl_3$.

(1) 4-Nitrodiphenylamine-2-carboxylic acid.

" 5- " " " "

" 4-Chloro " " "

(2) 3:4-Dimethoxy " "

(11) 2':4'-Dinitro " "

(3) 4-Nitro-3'-chloro " "

(3)/

(3) 4-Nitro-3'-bromo-2-carboxylic acid.

(12) 4-nitro-4'-methyl " " (c)

(3) 4-nitro-2'-methoxy " "

" 4-nitro-3'-methoxy " "

(13) 4-nitro-4'-methoxy " "

(14) 4-nitro-4'-aminodiphenylamine-2-carboxylic acid

(15) 5-nitro-3'-methyl " " "

" 5-nitro-4'-methyl " " "

" 5-nitro-4'-chloro " " "

" 5-nitro-4'-ethoxy " " "

(1) α-Naphthylphenylamine-2-carboxylic acid.

" β- " " " "

List of References in Table.

(1) Ullmann and co-workers. (Ber. 1906, 39, 169; Ann. 355, 312; C. 1908, I, 263)

(2) Borsche, Runge and Trautner. (Ber. 66, 1315).

(3) Present work.

(4) Tuttle. (J.A.C.S. 45, 1906)

(5) Nisbet. (J.C.S. 1932, 2772; 1933, 1372)

(6) Cohn. (Monatsh. 22, 385).

(7) /

(7) Bogert, Hirschfeld and Lauffer. (Coll. Czech. Chem. Comm. 2, 383).

(8) Schopf. (Ber. 25, 1930).

(9) Freund and Schwarz. (Ber. 56, 1828).

(10) Weiss. (Monatsh. 50, 109).

(11) Schroeter and Eisleb. (Ann. 367, 101).

(12) Kahn. (Ann. 279, 270).

(13) Lesnianski. (Bull. Acad. Polon. 1929. A. 31).

(14) Goldstein and Rodel. (Helv. Chim. Act. 9, 765).

(15) Lehmstedt. (Ber. 65, 999).

(a) 4'Ethoxydiphenylamine-2-carboxylic acid cyclised to yield 3-hydroxyacridone.

(b) In this case the cyclisation was carried out for 5 hours at 140° instead of the usual 100°.

(c) The reference is to the preparation of this compound. The cyclisation was attempted in the present work.

From/

From a consideration of the data in the two foregoing tables, some general regularities can be deduced.

A nitro group in the 4-, 4'-, and 5-positions prevents ring closure in sulphuric acid, exceptions being provided by the 2:4-dinitro compound (see note (b) above), and 4:4'-dinitro compound.

In one case the chloro group in the 4 position prevents ring closure, and in another the 3:4-dimethoxy groups.

The naphthyl group is also instrumental in this prevention.

The 4'-nitrodiphenylamine-2-carboxylic acid (Ullmann and Goldberg, Ber. 39, 169) does not cyclise either by the sulphuric acid method or by the PCl_5, $AlCl_3$ method. Ullmann and Goldberg do not mention its cyclisation, and Ullmann and Bader prepared 3-nitroacridone from the isomeric 4-nitrodiphenylamine-2-carboxylic acid. In the present research even when treated by the modified Friedel-Craft reaction with PCl_5 and $AlCl_3$, the acid was recovered unchanged.

EXPERIMENTAL II.

4'-Nitrodiphenylamine-2-carboxylic acid (cf. Goldberg, Ber. 1906, 39, 169).

The method of condensation used by Clemo, Perkin and Robinson (J. 1924, II, 1751) was employed. Anthranilic acid (6.3 gm.), p-nitrochlorobenzene (8 gm.), dry K_2CO_3 (7 gm.) and a trace of copper bronze powder were heated at 200°C. in an oil-bath until after the evolution of CO_2, the reaction mixture solidified to a dark red mass. On further heating for 2 hours, the mass became dark olive-green and viscous, finally resolidifying and remaining unchanged after further heating for an hour at the same temperature. The hard mass was cooled and extracted with hot water, filtered, and the filtrate steam distilled to remove excess p-nitrochlorobenzene. On acidifying the residual solution with hydrochloric acid in the hot a copious dark green precipitate was formed, was filtered, washed with hot water, and dried. 9.2 gm. (79% yield), m.p. 170°C. On recrystallisation from xylene, formed yellow crystals, m.p. 204°C.

(Goldberg/

(Goldberg m.p. 211°C.). The acid was pure enough for conversion to the 4'-aminodiphenylamine-2-carboxylic acid.

4'-Aminodiphenylamine-2-carboxylic acid.

(cf. Ullmann and Bader, Ann. 1907, 355, 335)

To a solution of 4'-nitrodiphenylamine-2-carboxylic acid (38 gm.) in 1 litre of water containing 150 c.c. concentrated NH_4OH solution (S.G. 0.88) heated on the water bath, was added $FeSO_4.7H_2O$ (252 gm.) in 1 litre of water containing 1 drop of concentrated sulphuric acid (to prevent slight hydrolysis of the $FeSO_4$ on heating) and the mixture kept at a temperature of 70°C. for 2 hours. After boiling for 15 minutes, filtering hot, and extracting the residue thrice with dilute NH_4OH solution, 4'-aminodiphenylamine-2-carboxylic acid was precipitated from the combined pale blue filtrates at its iso-electric point, by the addition of dilute hydrochloric acid. The well-washed, purplish-white precipitate which readily oxidises on heating, was dried to constant weight in the vacuum desiccator. The 4'-aminodiphenylamine-2-carboxylic acid/

acid m.p. 195°C. (recrystallised from xylene m.p. 204°C.) was pure enough for conversion to 3-amino-acridone. Yield 26 gm. (80% yield).

This acid was also prepared by the method of Ullmann and Bader by the condensation of o-bromo-benzoic acid with p-phenylenediamine in amyl alcohol solution in the presence of K_2CO_3 and copper catalyst. The yield (60%) on the large scale was poorer than by the previous method, and the product dark purple in colour melted at 185°C.

4'-Acetylaminodiphenylamine-2-carboxylic acid.

(cf. 4'-acetylaminodiphenylamine-2-carboxylic acid methyl ester. Goldstein and Rodel. Helv. Chim. Act. 9, 765).

o-Bromobenzoic acid (40 gm.) intimately mixed with p-aminoacetanilide (30 gm.) and dry K_2CO_3 (30 gm.) plus a trace of copper bronze powder (0.2 gm.) was heated under reflux in 200 c.c. amyl alcohol in an oil-bath at 155°C. for 4 hours. The amyl alcohol ~~and excess p-aminoacetanilide~~ was then removed by steam distillation and the cooled purple solution of the potassium salt carefully neutralised with dilute hydrochloric acid, in the cold/

cold to prevent hydrolysis of the acetylamino group. The dark purple precipitate was washed acid-free and dried on the water bath. Yield 49.2 gm. (88% yield), m.p. 210°C. Recrystallised from alcohol m.p. 230-231°C. Yield 44 gm. Thrice recrystallised from xylene, creamy-white needles, m.p. 240°C. (Found N, 10.4; $C_{15}H_{14}O_3N_2$ requires N = 10.4%).

4'-Acetylaminodiphenylamine-2-carboxylic acid is very soluble in absolute alcohol, acetone, ether and acetic acid, moderately soluble in hot xylene, and almost insoluble in benzene, ligroin and water.

4-nitro-3'-chlorodiphenylamine-2-carboxylic acid.

2-Bromo-5-nitrobenzoic acid (12 gm.) mixed with m-chloroaniline (7 gm.), dry K_2CO_3 (12 gm.) and a trace of copper powder, was heated in 100 c.c. amyl alcohol for $2\frac{1}{2}$ hours at 145-150°C. After the amyl alcohol had been distilled off in a current of steam, the solution was allowed to cool, when a red crystalline potassium salt separated as platelets. These were filtered off, washed with a little water, and after solution in 200 c.c. of hot water, converted to the acid by dilute hydrochloric/

hydrochloric acid. The greenish-yellow precipitate of the acid was filtered, washed acid-free, and dried. After recrystallisation twice from xylene yellow needles m.p. 258°C.
(Found N, 9.6%; $C_{13}H_9O_4NCl$ requires N = 9.6%); very soluble in alcohol and glacial acetic acid, and almost insoluble in ligroin and water.

4-Nitro-4'-bromodiphenylamine-2-carboxylic acid.
(cf. Papasogli, Atti. R. Accad. Lincei Rom. [5], 33 II, 106).

2-Bromo-5-nitrobenzoic acid (6 gm.), p-bromoaniline (4.5 gm.), dry K_2CO_3 (6 gm.) and a trace of copper powder, were heated in 20 c.c. amyl alcohol for 3 hours at 145-150°C. The resulting dark red solution was steam distilled to remove amyl alcohol and excess p-bromoaniline, and from the dark red solution on cooling an orange-red potassium salt crystallised in platelets. These were filtered off and recrystallised from boiling water by salting out with K_2CO_3. The potassium salt crystallised out on cooling, and was redissolved in 200 c.c. hot water and acidified with/

with dilute hydrochloric acid, when a dark green precipitate of the acid was formed. This precipitate was washed acid-free, dried, and re-crystallised from glacial acetic acid, dark green needles m.p. 284°C.
(Found N, 8.3; $C_{13}H_9O_4N_2Br$ requires 8.3%); very soluble in alcohol, moderately soluble in hot xylene and almost insoluble in water.

4-Nitro-4'-aminodiphenylamine-2-carboxylic acid.

(Kalle, D.R.P. 112,914; Goldstein and Rodel, Helv. Chim. Act. 9, 765, 1926).

2-Bromobenzoic acid (5 gm.), p-phenylene-diamine (2.5 gm.), dry K_2CO_3 (5 gm.) and a trace of copper bronze powder, were heated in 12 c.c. amyl alcohol on the water bath for fifteen minutes. The green mixture was steam distilled to remove amyl alcohol and excess p-phenylenediamine, and from dark solution dark red platelets of the potassium salt separated on cooling. These were filtered off, washed with a little water, and dissolved in 200 c.c. water. Dilute acetic acid was added in the hot to precipitate the acid as

a/

a greenish-yellow precipitate. Afterfiltering off, drying, and recrystallisation from xylene, the 4-nitro-4'-aminodiphenylamine-2-carboxylic acid formed light yellow crystals m.p. 225°C. (Goldstein and Rodel quote m.p. 226-227°C.).

4-Nitro-2'-methoxydiphenylamine-2-carboxylic acid.

2-Bromo-5-nitrobenzoic acid (12 gm.), o-anisidine (7 gm.), dry K_2CO_3 (12 gm.) and a trace of copper bronze powder, were heated in 50 c.c. amyl alcohol for 3½ hours at 145-150°C. The reaction mixture was steam-distilled to remove amyl alcohol and excess o-anisidine, and the solution heated with charcoal and filtered hot. To the hot solution dilute hydrochloric acid was added to precipitate the 4-nitro-2'-methoxydiphenylamine-2-carboxylic acid as a brown mass which was filtered off, and dried. After recrystallisation from xylene, the acid formed yellow needles, m.p. 210-211°C. (Found N = 10.1; $C_{14}H_{12}O_5N_2$ requires N = 10%); very soluble in alcohol and glacial acetic acid, moderately soluble in hot xylene, and benzene, and almost insoluble in ligroin and water.

4-/

4-Nitro-3'-methoxydiphenylamine-2-carboxylic acid.

2-Chloro-5-nitrobenzoic acid (10 gm.), m-anisidine (freshly redistilled)(7 gm.), dry K_2CO_3 (10 gm.) and a trace of copper powder, were heated in 100 c.c. amyl alcohol at 145-150°C. for 3 hours. The reaction mixture was steam distilled to remove amyl alcohol and excess m-anisidine. From the cooled solution, the yellow potassium salt separated in platelets on cooling, was filtered off, and washed with a little water. From the hot solution of the potassium salt in 200 c.c. water, dilute hydrochloric acid precipitated the 4-nitro-3'-methoxydiphenylamine-2-carboxylic acid as a light yellow mass which was filtered off, dried, and recrystallised from xylene. Yellow needles m.p. 255°C. (Found N, 9.8; $C_{14}H_{12}O_5N_2$ requires 9.7%); very soluble in alcohol and glacial acetic acid, and almost insoluble in benzene and water.

4-Nitro-4'-methoxydiphenylamine-2-carboxylic acid.

Lesnianski. Bull. Acad. Polon. 1929. A. 81.

2-Bromo-5-nitrobenzoic acid (2.5 gm.) p-anisidine (1.5 gm.),dry K_2CO_3 (2.5 gm.) and a trace of copper powder were heated for 3 hours on the water bath. The mixture melted and then slowly became/

became dark-green in colour. The melt was extracted with hot water and the excess p-anisidine distilled off in a current of steam. On neutralisation in the hot with dilute hydrochloric acid, 4-nitro-4'-methoxydiphenylamine-2-carboxylic acid separated as a dark-brown precipitate which was washed acid-free, and dried (2.5 gm. 86 % yield). Recrystallised from alcohol dark purple diamond-shaped platelets, m.p. 228°C. (Lesnianski 230.5°C.) (Found C, 57.9; H, 4.1; $C_{14}H_{12}O_5N_2$ requires C, 58.3%; H, 4.2%).

4-Nitro-4'-methyldiphenylamine-2-carboxylic acid.

(Kahn, Ann. 279, 270)

2-Bromo-5-nitrobenzoic acid (12 gm.), p-toluidine (11 gm.), dry K_2CO_3 (12 gm.) and a trace of copper powder heated at 145-50°C. in amyl alcohol solution (30 c.c.) for 1½ hours. The reaction mixture turned dark-brown. The amyl alcohol and excess p-toluidine were distilled off in a current of steam, and from the hot aqueous solution 4-nitro-4'methyldiphenylamine-2-carboxylic acid was precipitated as a brown mass by dilute hydrochloric acid. The acid was washed acid free, dried/

dried and recrystallised twice from xylene, yellow platelets, m.p. 262°C. The acid was very soluble in alcohol and glacial acetic acid, moderately soluble in hot xylene and slightly soluble in benzene and hot water.

2'-Methyl-5-nitro-diphenylamine-2-carboxylic acid.

Clemo, Perkin and Robinson (J. 1924, 1751) record the first preparation of this acid, but did not purify and analyse it. o-Chlorobenzoic acid (15.6 gm.), 4-nitro-2-aminotoluene (p-nitro-o-toluidine)(15.2 gm.), dry K_2CO_3 (7 gm.) were heated in amyl alcohol (50 c.c.) for 30 hours at 145-150°C. The amyl alcohol and excess p-nitro-o-toluidine were distilled off in a current of steam. 8% NaOH (70 c.c.) were added to residual solution, the mixture left to stand overnight, filtered, and acidified in the hot with dilute hydrochloric acid. Crude diphenylamine acid (15 gm.55% yield) separated as a brown precipitate, which was filtered off, and boiled with water to remove o-chlorobenzoic acid. The acid was then dissolved in 200 c.c. water to which the calculated amount of K_2CO_3 required to form the potassium/

potassium salt, had been added. Taking advantage of the low solubility of this salt in K_2CO_3 solution, K_2CO_3 was added to the hot red solution until "salting-out" separation just began. On cooling the salt separated as crimson rectangular platelets, these being filtered off, and redissolved in 200 c.c. water. From this solution, the acid was precipitated in the hot by dilute hydrochloric acid, filtered off, washed acid free, dried, and recrystallised twice from xylene. Orange red needles m.p. 206-207°C. (Found N, 10%; $C_{14}H_{12}O_4N_2$ requires N, 10.3%); very soluble in alcohol and glacial acetic acid, sparingly soluble in benzene and toluene, almost insoluble in water.

2'-Methyl-5'-aminodiphenylamine-2-carboxylic acid.

2'-Methyl-5-nitrodiphenylamine-2-carboxylic acid (2.7 gm.) was dissolved in ammonia (10 c.c.) in water (10 c.c.), heated to 70° on the water bath. To the clear red solution was added a solution of $FeSO_4,7H_2O$ (17 gm.) in water (20 c.c.) also heated to 70°. The resulting mixture was heated and stirred/

stirred at the same temperature for 1 hour, then boiled for 15 minutes to coagulate the ferric hydroxide precipitate, thus rendering the subsequent filtration more rapid. After filtration the ferric hydroxide was boiled thrice with hot dilute ammonia solution, and the combined pale brown filtrates brought to the isoelectric point of the amino acid with dilute hydrochloric acid. On standing in contact with the isoelectric solution the precipitate was slowly converted into brownish-white platelets, m.p. 190°C. (Found N, 11.2%; $C_{14}H_{14}O_2N_2$ requires 11.6%). Yield 1.8 gm. (75%).

3'-Nitrodiphenylamine-2-carboxylic acid.

(Ullmann and Bader. loc. cit.)

o-Chlorobenzoic acid (11.5 gm.), m-nitraniline (9.5 gm.). dry potassium carbonate (12 gm.) and copper powder (0.2 gm.) were heated for 4 hours in amyl alcohol (100 c.c.) under reflux at 145-150°C. The amyl alcohol was distilled off in a current of steam, and the dark brown solution left to cool. The excess m-nitraniline was filtered off and the filtrate made acid with hydrochloric acid, when a copious greenish-yellow precipitate was formed. The crude acid was filtered off, boiled with one litre of water to remove excess o-chlorobenzoic acid, dried, and washed with a little cold benzene. After drying the product weighed 15 gm. (89%,

Ullmann/

Ullmann 66%) and had m.p. 212° (Ullmann, pure m.p. 218°). This uncrystallised acid was pure enough both for conversion to the 3'aminodiphenylamine-2-carboxylic acid, and to 4-nitroacridone.

3'-Aminodiphenylamine-2-carboxylic acid.

(Ullmann and Bader, loc. cit.)

3'-Nitrodiphenylamine-2-carboxylic acid (13 gm.) was dissolved in water (300 c.c.) containing concentrated ammonia solution (50 c.c.) and heated to 70°C. on the water-bath. To the dark red solution was added with vigorous stirring, a solution of $FeSO_4.7H_2O$ (87 gm.) in water (200 c.c.) plus dilute sulphuric acid (1 drop), and the mixture heated at 70°C. for one hour. It was then boiled for 15 mins. and filtered. The ferric hydroxide residue was extracted twice with hot dilute ammonia solution, and the combined pale brown filtrates brought to the iso-electric point of the amino acid. The acid was precipitated as a grayish-white mass which was filtered off, and dried to constant weight in the vacuum desiccator. The 3'-aminodiphenylamine-2-carboxylic/

carboxylic acid weighed 11 gm. (95% yield) and had m.p. 164°C. (Ullmann, pure m.p. 166°).

3-Nitro-4'-methyldiphenylamine-2-carboxylic acid.

o-Chlorobenzoic acid (15.6 gm.), 2-nitro-4-aminotoluene (o-nitro-p-toluidine)(15.2 gm.), dry K_2CO_3 and a trace of copper powder, were heated in amyl alcohol (50 c.c.) at 145-150°C. for 30 hours. The amyl alcohol and excess o-nitro-p-toluidine distilled off in a current of steam, 8% NaOH solution (80 c.c.) added to residual solution, and the mixture left to stand overnight. The solution was filtered, heated, acidified with dilute hydrochloric acid, and the precipitated brown acid boiled with water to remove o-chlorobenzoic acid. The dried acid (16 gm.59% yield) had m.p. 187°C., and after recrystallisation twice from xylene formed yellow needles, m.p. 194-5°C. (Found N, 10.5. $C_{14}H_{12}O_4N_2$ requires 10.3%).

3'-Amino-4'-methyldiphenylamine-2-carboxylic acid.

3'-Nitro-4'-methyldiphenylamine-2-carboxylic acid (-3.5 gm.) was dissolved in a mixture of NH_4OH solution (0.88 S.G., 50 c.c.) and water (100 c.c.) heated to 70°C. on the water-bath. A solution of/

of $FeSO_4,7H_2O$ (84 gm.) in water (100 c.c.) was added rapidly with vigorous stirring to the ammonia solution, and the mixture heated on the water-bath for 1 hour after which it was boiled for 15 mins. to coagulate the $Fe(OH)_3$ precipitate. After filtration, the $Fe(OH)_3$ precipitate was extracted twice with hot dilute NH_4OH, and the pale brown combined filtrates brought to the iso-electric point of the amino acid. The cream coloured precipitate of 3'-amino-4'-methyl-diphenylamine-2-carboxylic acid was filtered off, washed, and dried to constant weight in a vacuum desiccator. (10.5 gm. 88% yield). m.p. 186°C. Recrystallised from xylene, creamy white platelets, m.p. 188°C. (Found N, 11.8. $C_{14}H_{14}O_2N_2$ requires N, 11.6%).

3-Aminoacridone.

(Ullmann and Bader. Ann. 355, 335)

4'-Aminodiphenylamine-2-carboxylic acid (26 gm.) was dissolved in 96% sulphuric acid (260 gm.) in the cold. The process occurred with the evolution of heat. On heating the dark solution in the water bath for 15 minutes, a powerful blue-green fluorescence developed, and when poured into a mixture of ice and water a dark-green solution was formed. This strongly acid solution was at first neutralised with concentrated NaOH solution. At a pH of about 3, a dark green precipitate consisting of 3-aminoacridone sulphate was formed. On continuing the process of neutralisation with NH_4OH solution, the mixture of sulphate and solution formed, on making the whole alkaline, a greenish yellow precipitate of 3-amino-acridone which was filtered off and washed first with Na_2CO_3 solution to remove traces of unconverted acid and then with water. After drying, the base (23 gm. 96% yield) was re-crystallised from alcohol or methylated spirit (industrial) when it formed yellow needles, m.p. 298°C. 3-Aminoacridone is very soluble in alcohol/

alcohol, and acetone, difficultly soluble in benzene and toluene, insoluble in water and ligroin. In concentrated sulphuric acid the base is very soluble, and shows a powerful blue-green fluorescence, in concentrated hydrochloric acid it has a slight solubility, a pale-green hydrochloride is formed, and in concentrated sodium hydroxide solution the base shows a slight and unexpected solubility, probably due to the enolisation of the central keto group.

Cyclisation of 4'-acetylaminodiphenylamine-2-carboxylic acid by means of concentrated sulphuric acid.

4'-Acetylaminodiphenylamine-2-carboxylic acid (40.5 gm.) was heated with 96% sulphuric acid (200 c.c.) at 100°C. in the water-bath for 3 hours, when a powerful blue-green fluorescence had developed. It was then poured on to about 400 gm. of ice and the whole reheated for 2 hours to effect complete hydrolysis of the acetylamino group. On cooling and partial neutralisation the gray-green crystals of 3-aminoacridone sulphate which separate are filtered off. A small quantity of the base is obtained by complete neutralisation of the mother liquor/

liquor. The sulphate is converted into the base by means of dilute ammonia solution. Yield of crude aminoacridone (m.p. 290°C.), 29.2 gm. Recrystallised from absolute alcohol, m.p. 297°C.

3-Acetaminoacridone.

(cf. Goldstein and Rodel, Helv. Chim. Act. 9, 765)

3-Aminoacridone (5.25 gm.) was dissolved in glacial acetic acid (50 c.c.) and acetic anhydride (2.55 gm.) added. The mixture was boiled for half an hour. On cooling green crystals of the 3-acetamido-acridone separated out, were filtered off, and washed acid free with water. Yield 5.89 gm. (93%). The compound was recrystallised from nitrobenzene when it formed greyish-white needles m.p. 397° (Goldstein and Rodel quote no m.p. below 340°C.).(Found C, 71.2; H, 4.8. $C_{15}H_{12}O_2N_2$ requires C, 71.4%; H, 4.8%).

Nitro-3-acetamidoacridone.

3-Acetamidoacridone (6 gm.) was dissolved in concentrated sulphuric acid (30 c.c.) and cooled to 0-5°. A mixture of 68.6% nitric acid (1.7 c.c) and concentrated sulphuric acid (5 c.c.) was slowly added with stirring, keeping the temperature between the limits/

limits previously mentioned. The stirring was continued for one hour after the completion of the addition of the nitrating mixture. The resulting solution was poured on to ice (200 gm.) when a brownish-yellow precipitate was formed. This was filtered off, dried, and recrystallised from glacial acetic acid. Yield 4.6 gm. recrystallised. The nitro-3-acetamidoacridone formed yellow needles having no m.p. below 400°C. (Found N, 13.9. $C_{15}H_{11}O_4N_3$ requires N, 14.1%).

Nitro-3-aminoacridone.

Nitro-3-acetaminoacridone (2.45 gm.) was dissolved in 50% sulphuric acid (50 c.c.) and heated on the water-bath for one and a half hours. The greenish-brown solution turned dard red and on cooling, yellow crystals of the sulphate separated out. The solution was diluted and made alkaline with Na_2CO_3 solution. A dard red precipitate of the base was formed, filtered off, and dried. After recrystallisation from nitro-benzene, the (?) nitro-3-amino-acridone formed crimson needles having no m.p. below 400°C. (Found 16.1. $C_{13}H_9O_3N_3$ requires 16.5%).

This had the peculiarity of being almost equally soluble in acids and strong alkalies, forming pale yellow/

yellow solutions with the former and deep crimson red solutions in the latter. On diazotisation of the acid solution with sodium nitrite, and subsequent coupling with sodium β-naphtholate, a good red diazo is obtained.

4-Nitroacridone.

(Ullmann and Bader, loc. cit.)

3-Nitrodiphenylamine-2-carboxylic acid (14 gm.) was dissolved in 96% sulphuric acid (90 c.c.) and heated at 100° in the water-bath for one and a half hours. The resulting solution was cooled and poured into water (500 c.c.) when a greenish yellow precipitate was formed. The crude 4-nitroacridone was filtered off, washed with Na_2CO_3 solution and dried. 13 gm. (theoretical yield) m.p. 330-335°. Recrystallised from nitrobenzene yellow needles, m.p. 336°. (First recorded m.p. for 4-nitroacridone. 4-Nitroacridone formed a reddish-orange solution in alcoholic KOH solution.

4-Aminoacridone.

(Ullmann and Bader, loc. cit.)

4-Nitroacridone (8.7 gm.) was suspended in absolute alcohol (200 c.c.) and a mixture of stannous chloride (25 gm.) and concentrated hydrochloric acid (33 c.c./

(33 c.c.) added. The mixture was heated under reflux on the water-bath until complete solution had taken place. The filtered alcoholic solution was diluted to one litre with water and more hydrochloric acid (50 c.c.) added. This solution was heated to boiling point and H_2S passed in. A copious brown precipitate of stannous sulphide was formed. This was filtered off and extracted twice with hot dilute hydrochloric acid. To the combined filtrates resaturated in the hot with H_2S, ammonia solution was added until the solution was alkaline, when a yellow precipitate was formed. This precipitate was filtered off, washed with water, and dried. m.p. 275°. Recrystallised from aqueous alcohol yellow needles, m.p. 289-290°. The yield by this method was very poor.

3'-Aminodiphenylamine-2-carboxylic acid (11 gm.) was dissolved in 96% sulphuric acid and heated for one and a half hours in the water-bath at 100°. The resulting fluorescent dark-green solution was poured into water (600 c.c.) and made alkaline with NaOH solution. A brown sulphate was precipitated when the solution was weakly acid. The yellow 4-amino-

acridone/

acridone was filtered, washed with Na_2CO_3 solution and dried. 8.3 gm. m.p. 285°. Recrystallised from aqueous alcohol the aminoacridone had m.p. 290-291°. A mixed m.p. with the aminoacridone prepared in the previous manner gave 289-291°. Both substances dissolved in alcohol to give a yellow solution which on the addition of hydrochloric acid developed a brilliant green fluorescence.

3-Bromo-7-nitroacridone.

(Lehmstedt. Ber. 1932, 65, 999).

4-Nitro-4'-bromodiphenylamine-2-carboxylic acid (3.4 gm.) was dissolved in nitrobenzene and PCl_5 (41 gm.) added. The mixture was heated on an oil-bath at 150°C. until no further evolution of hydrochloric acid gas was observed. After cooling, $AlCl_3$ (5 gm.) were added in small portions with cooling. A further evolution of hydrochloric acid gas occurred, and the mixture was again heated at the same temperature until no further hydrochloric acid gas was given off. After pouring on to ice, to decompose excess PCl_5 and $AlCl_3$, the mixture of nitrobenzene and water was steam-distilled to remove the nitro-benzene. On filtering a brownish-green precipitate of the 3-bromo 7-nitroacridone was obtained. This was washed with/

with Na_2CO_3 solution to remove traces of unconverted diphenylamine acid, then with water, and dried (3 gm.) no m.p. below 400°C. Recrystallised from nitrobenzene small greenish-yellow needles, no m.p. below 400°C. (Found N, 8.6; Br, 23.9; $C_{13}H_7O_3N_2Br$ requires N, 8.8%; Br, 25%). The nitrobromoacridone was soluble in glacial acetic acid, and nitrobenzene, slightly soluble in alcohol and benzene, insoluble in water, and dissolved in concentrated NaOH solution to a slight extent to give a red solution.

2-Amino-3-methylacridone.

3'-Amino-4'-methyldiphenylamine-2-carboxylic acid (5 gm.) was dissolved in 96% sulphuric acid (50 gm.), solution occurring with the evolution of some heat. The dark-brown solution was heated in the water-bath for half an hour at 100°C., and then poured on to ice. From the orange solution on making alkaline with NH_4OH solution, a yellow precipitate of 2-amino-3-methylacridone was obtained, and is washed with Na_2CO_3 solution, then with water, and dried (3.65 gm. 82% yield). Recrystallised from aqueous alcohol, the base formed clusters of greenish-white needles, m.p. 320°C. (Found N, 12.1. $C_{14}H_{12}ON_2$ requires N, 12.5%). The pale yellow alcoholic/

alcoholic solution fluoresced weakly purple. On the addition of hydrochloric acid to this solution an intense green fluorescence developed. In 10% NaOH solution, the base dissolved to a slight extent forming a pale yellow solution fluorescing blue. On adding $NaNO_2$ solution, to the base dissolved in dilute hydrochloric acid, a deep red solution was formed, which on addition to sodium β-naphtholate solution, precipitated a bright red azo compound.

3-Methyl-4-nitroacridone.

3'-Nitro-4'-methyldiphenylamine-2-carboxylic acid (0.3 gm.) was dissolved in 96% sulphuric acid (5 c.c.) and heated in the water-bath at 100°C. for half an hour. The solution was then poured on ice, and the yellow nitromethylacridone precipitated, filtered off, and washed with Na_2CO_3 solution and water. Yield 0.23 gm. (82%). Recrystallised from nitrobenzene, the 3-methyl-4-nitroacridone formed clusters of light yellow needles, m.p. 330-331° decomp. (Found N, 10.8. $C_{14}H_{10}O_3N_2$ requires 11%). The nitroacridone dissolved in alcoholic KOH solution to give an orange-red solution.

3-/

3-Methyl-4-aminoacridone.

3-Methyl-4-nitroacridone (0.13 gm.) was suspended in absolute alcohol (10 c.c.) containing hydrochloric acid (1 c.c.) and stannous chloride (0.54 gm.) and heated until complete solution took place to form an orange- non-fluorescent solution. On cooling and adding dilute ammonia solution a copious orange precipitate was formed. The orange precipitate was filtered off and dried, no m.p. below 400°. This compound proved to be the tin salt of the base as on performing a combustion test a white residue of stannic oxide was formed. The tin salt was redissolved in alcoholic hydrochloric acid solution and H_2S passed in until no more of the brown precipitate of stannous sulphide was formed. After filtration, the alcoholic solution was made alkaline with dilute ammonia solution when a bright greenish-yellow precipitate was formed. This was filtered off and dried. m.p. 250°C. After solution in acetic acid and reprecipitation by dilute ammonia solution, the 3-methyl-4-aminoacridone had m.p.250°C. and showed a tendency to oxidise on heating, turning emerald-green. (Found N, 12.4;$C_{14}H_{12}ON_2$ requires N, 12.5%). The solution in alcohol was yellow and non-fluorescent/

fluorescent. On addition of dilute hydrochloric acid the solution became pale yellow, no fluorescence developing. The solution of the base in 10% NaOH was yellow and non-fluorescent. The solution of the diazo compound, formed by the addition of $NaNO_2$ solution to the hydrochloric acid solution of the base, was orange, and formed a slight reddish-brown precipitate on coupling with sodium β-naphtholate solution.

1-Methyl-4-aminoacridone.

2' Methyl-5'-aminodiphenylamine-2-carboxylic acid (1.8 gm.) was heated in solution in 96% sulphuric acid (9 c.c.) for 1 hour at 100° in the water-bath. The solution was poured onto ice and water (50 c.c.) and made alkaline with dilute NaOH solution . A yellow sulphate changing to the brownish-yellow amino-acridone was formed. The 1-methyl-4-aminoacridone was filtered off and dried, m.p. 230°. After re-crystallisation from aqueous alcohol the compound had m.p. 231°C. (Found N, 12.4. $C_{14}H_{12}ON_2$ requires N, 12.5%). The alcoholic solution was yellow and non-fluorescent. On addition of hydrochloric acid, the solution became pale yellow, no fluorescence developing/

developing. By the addition of $NaNO_2$ solution the diazo compound solution which was orange, was formed from the aqueous hydrochloric acid solution. The diazo solution coupled weakly with sodium β-naphtholate solution precipitating a purple azo compound.

Attempted Cyclisation of a Series of Substituted 4-nitrodiphenylamine-2-carboxylic acids.

Each of the acids (1 gm.) listed below was heated at 100° for 3-5 hours with 96% sulphuric acid (10 c.c.). In each case the diphenylamine acid was recovered unchanged.

4'-nitrodiphenylamine-2-carboxylic acid.
4-nitro-4'-aminodiphenylamine-2-carboxylic acid.
4-nitro-3'-chlorodiphenylamine-2-carboxylic acid.
4-nitro-4'-bromo " "
4-nitro-2'-methoxy " "
4-nitro-3'-methoxy " "
4-nitro-4'-methoxy " "
4-nitro-4'-methyl " "

III. PREPARATION OF ACRIDONE ARSONIC ACIDS

Three methods for the preparation of acridone arsonic acids, presented themselves, corresponding to the three stages in the synthesis of the acridone nucleus at which it was possible to introduce the arsonic acid group.

(1) A substituted phenyl arsonic acid might be condensed to form an o-carboxydiphenylaminearsonic acid, which might be cyclised to the acridone arsonic acid.

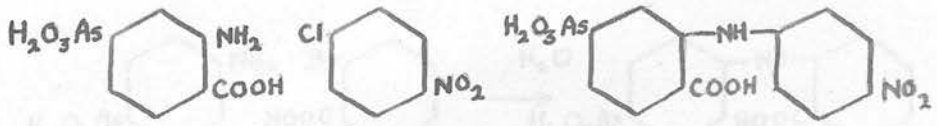
(2) An o-carboxyaminodiphenylamine might be treated by the Bart reaction to give an o-carboxydiphenylaminearsonic acid, with subsequent cyclisation as above. No o-carboxydiphenylaminearsonic acids have yet been synthesised by this method, although Burton and Gibson (J. 1926, 460), Gibson and Johnson (ibid. 1928, 1286) prepared N-acetyldiphenylamine-4-arsonic acid by means of a Bart reaction on N-acetyl-p-amino-diphenylamine.

(3) By means of the Bart reaction, an aminoacridone might be converted to an acridone arsonic acid.

Method/

Method (1) has four subdivisions:

(a) A 1-amino-2-carboxyphenylarsonic acid

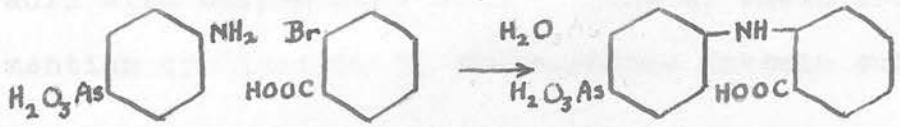


VI.

might be condensed with a halogenobenzene in which the halogen is activated by the means of a nitro-group. In this present work, 3-amino-4-carboxy-phenylarsonic acid (VI) was heated in amyl alcohol solution in presence of K_2CO_3 and copper catalyst, with o-nitrochlorobenzene, p-nitrochlorobenzene, p-nitrobromobenzene, and 2:4 dinitro-1-chlorobenzene. Condensation to the diphenylamine derivatives did not take place. No diphenylamine-5-arsonic acids are recorded in the literature. Gibson and Johnson (J. 1927, 2499; 1928, 1286; 1929, 1229) and Wintersteiner and Lieb (Ber. 1928, 61, 107 and 1126) prepared a large number of o-arsanilic acid derivatives, and these workers state a greater yield is obtained in these cases by the condensation of a nitrohalogenobenzene with o-arsanilic acid, than by the condensation of a nitraniline with an o-halogenophenylarsonic acid.

(b) /

(b) An aminophenylarsonic acid might be condensed with an o-halogenobenzoic acid,



the halogen being activated by the carboxy group in the o-position. In this work, p-aminophenylarsonic acid (p-arsanilic acid) was heated in amyl alcohol solution as previously described for the amino-carboxyphenylarsonic acid, with 2-bromo-5-nitrobenzoic acid. No condensation to the diphenylaminearsonic acid took place, the p-arsanilic acid being recovered unchanged, and the nitrobromobenzoic acid being partially obtained as 5-nitrosalicylic acid.

(c) A halogenophenylarsonic acid might be condensed with an o-aminobenzoic acid.

Burton and Gibson (J. 1927, 247) and Barber (ibid. 1929, 471) employed this method, the former workers condensing o-bromophenylarsonic acid with the/

the three isomeric aminobenzoic acids, and the latter condensing 4-chloro-3-nitro-phenylarsonic acid with anthranilic acid. None of these workers mention cyclisation to the acridone arsonic acids.

(d) A 1-halogeno-2-carboxyphenylarsonic acid might be condensed with an amine. This method has not yet been attempted.

It would appear from the data quoted in the literature, and the results obtained in this research that early introduction of the arsonic acid group in the synthesis of acridone arsonic acids is unprofitable. The arsonic acid group has a "damping" effect similar to, but greater than the nitro group, on the reactivity of substituents in the same phenyl nucleus, thus it weakens the basicity of an amino group, this effect being least when the basic group is in the m-position to the radical containing arsenic. By theory and analogy with the nitro group, the arsonic acid group should activate halogeno groups in the o- and p- positions. From results it would seem that this activation is partly annulled by/

by the general effect of the arsonic acid group to reduce reactivity of the whole phenyl nucleus.

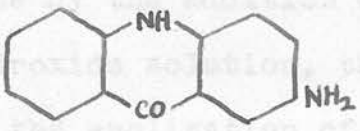
From the data and results quoted in Part II in connection with the cyclisation of diphenylamine-o-carboxylic acids it will have been seen that the nitro group prevents cyclisation by sulphuric acid when in the 3, 4, and 4' positions. It would not be too unreasonable to assume that, by analogy, the arsonic acid group would act similarly, and have an even greater effect owing to its more powerful general damping effect on reactivity.

To be added to these theoretical considerations, are the practical difficulties involved in working with arsonic acids. Their low solubility in organic solvents, their tendency to separate in a colloidal form, and their low reactivity render it advisable to bring them into the scheme of synthesis at as late a stage as possible.

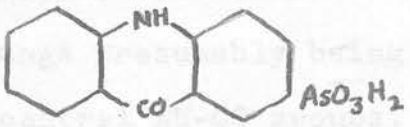
The approach to the acridone arsonic acids by method (3) has given the best results. The only previously recorded reference to the preparation of an arsenical acridine derivative is contained in American/

American Patent 1408974 in which 3:6 diamino-10-methylacridinium chloride was diazotised and treated with sodium arsenite solution, a reddish-brown powder resulting.

It was decided to synthesise 3-aminoacridone (Ullmann and Bader, Ann. 1907, 355, 335) and subject it to the Bart reaction.



IX.



XXX.

The acridone nucleus is numbered as shown. Only aminoacridones having the amino group in positions 2, 3, or 4 are useful, as the 1-amino-acridone condenses on diazotisation to form an acridone-triazole (Clemo, Perkin and Robinson (J. 1924, II, 1751), thus preventing the introduction of the arsonic acid group.

3-Aminoacridone (cf. Part II) was prepared and purified by recrystallisation from alcohol. The light greenish-yellow crystals were then pure enough/

by the general effect of the arsonic acid group to reduce reactivity of the whole phenyl nucleus.

From the data and results quoted in Part II in connection with the cyclisation of diphenylamine-o-carboxylic acids it will have been seen that the nitro group prevents cyclisation by sulphuric acid when in the 3, 4, and 4' positions. It would not be too unreasonable to assume that, by analogy, the arsonic acid group would act similarly, and have an even greater effect owing to its more powerful general damping effect on reactivity.

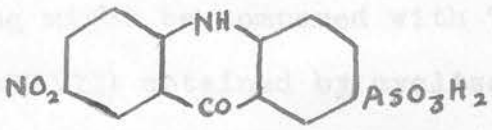
To be added to these theoretical considerations, are the practical difficulties involved in working with arsonic acids. Their low solubility in organic solvents, their tendency to separate in a colloidal form, and their low reactivity render it advisable to bring them into the scheme of synthesis at as late a stage as possible.

The approach to the acridone arsonic acids by method (3) has given the best results. The only previously recorded reference to the preparation of an arsenical acridine derivative is contained in American/

Na_2CO_3 solution. From the mother liquor, after filtration, on standing overnight, very small quantity of the acid separated in a crystalline form, having however all the other properties of the gelatinous variety. It formed a red solution in Na_2CO_3 solution, which deepened to a dark crimson red on the addition of sodium hydroxide solution, this effect being probably due to enolisation, either of the CO group to C.OH(Na) or of the nitro group

The position of entry of the nitro group into the acridone nucleus was not known, and the following experiments were carried out in order if possible to ascertain its position. It seemed probable that owing to the known damping effect of the arsonic acid on the reactivity of an aromatic ring to which it was attached, that the nitro group would enter in the unsubstituted ring of the acridone nucleus, forming most probably a 7-nitro-acridone-3-arsonic acid due to the m-directing effect of the keto group reinforcing the p-directing/

directing influence of the NH group.

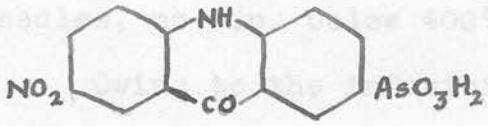


XXXI.

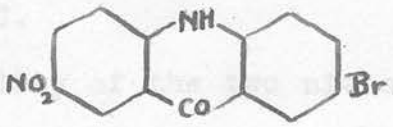
An attempt was therefore made to synthesise 7-nitro-3-aminoacridone from which by a Bart reaction the 7-nitro-acridone-3-arsonic acid might be prepared. 2-Bromo-5-nitrobenzoic acid was condensed in amyl alcohol solution in the previously described manner, with p-phenylenediamine and the 4-nitro-4'aminodiphenylamine-2-carboxylic acid (D.R.P. 112,914) so obtained, treated with 96% sulphuric acid at 100°C. to effect cyclisation. The nitro-amino acid did not cyclise to the desired nitro-aminoacridone (cf. Part II). This means of identification having proved fruitless, an attempt was made to utilise the degradation method of Schuster (Compt. rend. 1932, 195, 611). This worker has discovered that on boiling phenyl-arsonic acids with fuming hydrobromic acid, the arsonic acid group was replaced by the bromo group.

It seemed of interest to treat the nitro-acridone/

acridone 3-arsonic acid (XXXI) in the same way, in the hope that the nitro-3-bromoacridone possibly resulting might be compared with 7-nitro-3-bromo-acridone(XXVII) obtained by cyclisation of 4-nitro-4'bromodiphenylamine-2-carboxylic acid (XXVI)



XXXI.

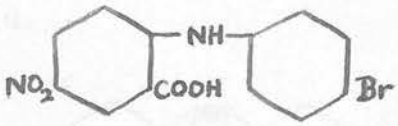


XXVII.

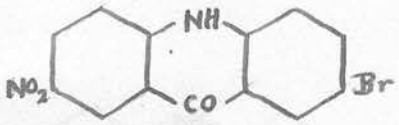
The fuming HBr (D = 1.6) was prepared by passing into HBr gas into the normal fuming acid (D = 1.42) below 0°C. Even on prolonged boiling at atmospheric pressure with this fuming HBr, the arsonic acid group was not replaced by the bromo group in the case of nitroacridone-3-arsonic acid. On heating the arsonic acid however with the HBr in a sealed tube at 125°C. for 6 hours, a product was obtained which was insoluble in Na_2CO_3 solution, contained bromine, and had no m.p. below 400°C.

7-Nitro-3-bromoacridone (XXVII) was obtained by cyclisation of 4-nitro-4'-bromodiphenylamine-2-carboxylic acid (XXVI) cf. Part II, by means of phosphorus pentachloride and aluminium chloride in nitrobenzene according to the method of Lehmstedt (Ber. /

(Ber. 1932, 999). Cf. Part II.



XXVI.



XXVII.

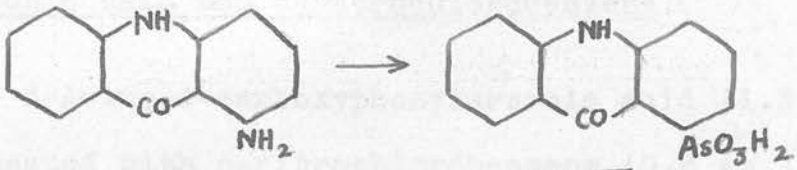
The nitrobromoacridone formed greenish-yellow needles, no m.p. below 400°C.

Owing to the infusibility of the two nitrobromoacridones below 400°C., identification was rendered inconclusive. Both compounds had similar crystalline form - sheaves of yellow needles and the same approximate solubilities in various organic solvents. They differed slightly in colour, the nitro-3-bromoacridone was orange-yellow; the 7-nitro-3-bromoacridone greenish-yellow.

4-Aminoacridone (XVII) was treated by the Bart reaction in the same way as described for the preparation of acridone-3-arsonic acid from 3-aminoacridone, and yielded the yellow amorphous acridone-4-arsonic acid (XXXII). This compound showed the same fluorescences in the weak, and strong alkalies, and in hydrochloric and sulphuric acids as its isomer.

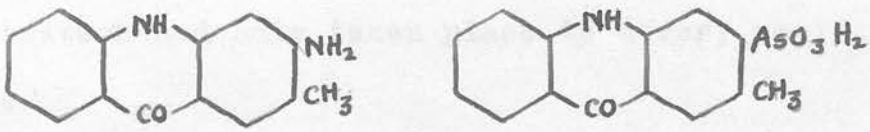
It/

It appeared to be rather more soluble in dilute hydrochloric acid and in hot water than acridone-3-arsonic acid.



XVII . XXXII .

2-Amino-3-methylacridone (XXV) was converted in the same manner by the Bart reaction to 3-methylacridone-2-arsonic acid(XXXIII) which formed an orange amorphous powder. Its solution in Na_2CO_3 solution was red with purple fluorescence, that in sodium hydroxide solution being red with a green fluorescence. In hydrochloric and concentrated sulphuric acids, the same green fluorescence appeared.



XXV . XXXIII .

Acridone-3-arsonic acid has been tested in virtue of its chemotherapeutic action on trypanosomes. It proved to be very toxic to the host. Acridone-4-arsonic acid and 3-methylacridone-2-arsonic acid have yet to be tested for their chemotherapeutic action.

EXPERIMENTAL III.

Attempted condensation of 3-amino-4-carboxyphenylarsonic acid and o-nitrochlorobenzene.

3-Amino-4-carboxyphenylarsonic acid (1.3 gm.) was heated with o-nitrochlorobenzene (0.8 gm.), dry K_2CO_3 (4 gm.) and a trace of copper bronze powder, in amyl alcohol (18 c.c.) at 145-150°C. for 7 hours. The dark solution was steam distilled to remove excess o-nitrochlorobenzene. On acidification with HCl to pH 2 (litmus and congo both red) a very small amount of a gelatinous material was precipitated. The filtrate fluoresced strongly and gave a positive diazo reaction. The main portion of the phenylarsonic acid was recovered unchanged. The condensation had only taken place to a very small extent.

Gibson (J. 1926, 40; 1928, 1286) obtained 2-nitrodiphenylamine-6'arsonic acid by heating o-arsanilic acid and o-nitrochlorobenzene to 110°C. When these reactants were heated in another experiment to 145-150°C. he obtained a gelatinous material similar to the above. The condensation was therefore repeated at this lower temperature.

3-/

3-Amino-4-carboxyphenylarsonic acid (0.5 gm.) was heated with o-nitrochlorobenzene (0.5 gm.) dry K_2CO_3 (0.5 gm.) and a trace of copper powder for 1 hour at 110°C. The cooled melt was filtered, and the red coloured filtrate neutralised with HCl and then brought carefully to pH 2. The solution fluoresced strongly and gave a strong positive diazo reaction. A very small quantity of a cream coloured compound was precipitated. The majority of the original arsonic acid was recovered unchanged. The condensation again did not seem to have taken place to any marked extent.

Attempted condensation of 3-amino 4-carboxyphenylarsonic acid with p-nitrochlorobenzene.

3-Amino-4-carboxyphenylarsonic acid (1 gm.) was heated with p-nitrochlorobenzene (3 gm.), dry K_2CO_3 (4 gm.) and a trace of copper powder for 1 hour at 200°C. The cooled dark melt was extracted with hot water, and the extract steam distilled to remove excess p-nitrochlorobenzene. A crystalline precipitate separated from the solution on cooling, was filtered off, washed, and dried. This

yellow/

yellow-brown substance (0.8 gm.) was recrystallised from ligroin, when it formed yellow needles, m.p. 142°C. From its properties and m.p. it was clearly identical with pp'-dinitrodiphenylether, m.p. 142.5-143°C. The p-nitrochlorobenzene had been presumably partially converted to p-nitrophenol, which had combined with the remaining p-nitrochlorobenzene to form the ether. The filtrate was acidified and the phenylarsonic acid was recovered unchanged. The condensation had not taken place.

The experiment was repeated in amyl alcohol solution at 145-150°C. with the same result, formation of a small amount of pp'-dinitrodiphenyl ether, m.p. 142°C. and recovery of the phenylarsonic acid unchanged.

Attempted condensation of 3-amino-4-carboxyphenylarsonic acid with p-nitrobromobenzene.

It was thought that the p-nitrobromobenzene might react more readily than the p-nitrochloro compound. 3-Amino-4-carboxyphenylarsonic acid (1 gm.) was heated in amyl alcohol (18 c.c.) with p-nitrobromobenzene (1 gm.). dry K_2CO_3 (4 gm.) and copper powder for 8 hours at 145-150°C. After steam/

steam distillation of the resulting solution to remove amyl alcohol and excess p-nitrobromobenzene, the alkaline solution was acidified and a very small amount of gelatinous material was precipitated. The majority of the p-nitrobromobenzene was recovered unchanged by the steam distillation, and the phenylarsonic acid was obtained unchanged from the filtrate.

Attempted condensation of 3-amino-4-carboxyphenylarsonic acid with 1:2:4 chlorodinitrobenzene.

It was known that the presence of two nitro groups in the 2:4 positions increased the reactivity of a halogen in the 1 position in the phenyl nucleus. An attempt was therefore made to determine whether the condensation would take place with this very reactive halogen atom in 1:2:4 chlorodinitrobenzene.

3-Amino-4-carboxyphenylarsonic acid was heated in amyl alcohol (18 c.c.) with 1:2:4 chlorodinitrobenzene, dry K_2CO_3 (4 gm.) and copper powder, for 8 hours at 145-150°C. The resulting mixture was steam distilled to remove amyl alcohol and excess 1:2:4 chlorodinitrobenzene, and the solution acidified with HCl. A yellowish-brown crystalline precipitate/

precipitate was formed, which after reprecipitation from alkali with acid and recrystallisation from ligroin, m.p. 113°C., proved to be dinitrophenol (1:2:4), m.p. 114°C. The filtrate on treatment yielded phenylarsonic acid unchanged. The condensation had not taken place.

Acridone-3-arsonic acid.

3-Aminoacridone (2.1 gm.) was dissolved in hot HCl (4.5 c.c. D. 1.19). $NaNO_2$ (0.8 gm.) in hot water (4 c.c.) was added drop by drop to the solution cooled below 0° C. The greenish hydrochloride disappeared and bright yellow crystals of the diazo compound separated. After standing for 30 minutes at 0°C. after the addition of the nitrite, the solution was neutralised at 0°C. with NaOH solution (5 N.). 13 c.c. of a solution containing arsenious oxide (1.5 gm.) in NaOH solution (5 N : 3 c.c.) and Na_2CO_3 (3 gm.) in water (9 c.c.), plus 0.3 c.c. of a 10% $CuSO_4.4NH_3.H_2O$ solution as catalyst (Burton and Gibson, J. 1929, 2386) was added when a steady evolution of N_2 occurred. After standing overnight at room temperature, the mixture was heated to 40°C. for a short time to ensure that the/

the reaction was complete, and filtered hot, the residue being extracted thrice with hot NaOH solution (5%). The combined filtrates which exhibit a powerful purple fluorescence were brought to pH 3 when the acid was precipitated as a yellow amorphous compound. It was purified by repeated solution in and reprecipitation from cold dilute Na_2CO_3 solution. Yield 1.33 gm. (42% calculated on theoretical yield). Found As, 22.8. $C_{13}H_{10}O_4NAs$ required 23.5%).

Acridone-3-arsonic acid forms a yellow amorphous powder which could not be obtained crystalline. It is slightly soluble in boiling glacial acetic acid, but separates on cooling in an amorphous form. Solutions of this acid in aqueous Na_2CO_3 or NaOH showed a characteristic powerful purple fluorescence even on great dilution. In strong NaOH solution, the fluorescence alters to bluish-green, a change probably associated with enolisation of the CO group. The acid is slightly soluble in cold concentrated HCl, and very soluble in concentrated sulphuric acid with a bluish-green fluorescence in both cases.

The metallic salts were prepared by adding the/

the appropriate reagent to the neutral solution of the salt.

The pale yellow mercuric salt, the yellow calcium salt, and the yellow lead salt separated in the cold in a gelatinous mass and appeared to become semicrystalline after boiling and cooling the solutions. The pale yellow semicrystalline barium salt and the pale yellow crystalline magnesium salt separated on cooling the boiled solution. The greenish-yellow amorphous cupric salt and the brown amorphous ferric salt separated in the cold.

7(?)Nitroacridone-3-arsonic acid.

Acridone-3-arsonic acid (1 gm.) was dissolved in concentrated sulphuric acid (5 c.c.) and the mixture cooled below 0°. A mixture of concentrated nitric acid (1.2 c.c. d: 1.43) and concentrated sulphuric acid (25 c.c.) was added drop by drop, keeping the temperature below 0°. After standing overnight, the reaction mixture was poured on to ice (100 gm.). The orange gelatinous precipitate formed was coagulated by boiling, and filtered off (1.1 gm.). The orange nitroacridone-3-arsonic acid/

acid (no m.p. below 400°C.) was purified by repeated solution in Na_2CO_3 solution, and regeneration by means of dilute hydrochloric acid. From the dilute nitric-sulphuric acid filtrate from the first precipitation a small quantity crystallised out on standing, in yellow sheaves. No difference in properties between the amorphous and the crystalline material could be observed. The acid formed an orange-red solution in Na_2CO_3 solution, which deepened to crimson on the addition of NaOH. (Found As, 20.7; $C_{13}H_9O_6N_2As$ requires 20.6%).

Degradation of 7(?)-nitroacridone-3-arsonic acid

7(?)-Nitroacridone-3-arsonic acid (1 gm.) was sealed up in a bomb-tube along with fuming hydrobromic acid (20 c.c.) (saturated at 0° with HBr gas) and heated at 125° for 5 hours. After cooling and cautious unsealing the bomb-tube, the contents were made alkaline with Na_2CO_3 solution and filtered. A small amount (0.2 gm.) of orange material proved insoluble in the alkali. This was recrystallised from nitrobenzene, forming orange needles with no m.p. below 400°. The compound contained bromine and no arsenic. A microanalysis performed by Dr Schoeller/

Schoeller confirmed the presence of bromine, but the bromine content was low, and the figures appeared to indicate the presence of nitrohydroxyacridone.

Acridone-4-arsonic acid.

4-Aminoacridone (4.2 gm.) in concentrated hydrochloric acid (18 c.c.) was cooled to 0° and diazotised by the addition of sodium nitrite (1.4 gm.) in water (10 c.c.). The aminoacridone formed a pale yellow hydrochloride which dissolved up to yield a dark red diazo solution. After standing for half an hour, the solution was made neutral by the addition of 5% sodium hydroxide solution, and 26 c.c. of the arsenite solution described in the preparation of acridone-2-arsonic acid, added. The mixture was left to stand overnight, then heated to about 30° to ensure the completion of the reaction, and filtered. From the orange filtrate which had an intense purple fluorescence, the yellow acridone-4-arsonic acid was precipitated by acidification with dilute hydrochloric acid. This precipitate was washed, redissolved in cold Na_2CO_3 solution, and re-precipitated with dilute acetic acid. (Found As, 23.7/

23.7; $C_{13}H_{10}O_4NAs$ requires 23.5%). By extraction of the red residue from the first filtration with 5% sodium hydroxide solution, a further quantity of less pure acid was obtained. This was purified by repeated solution in Na_2CO_3 solution and regeneration with dilute hydrochloric acid.

The acid formed a yellow amorphous powder, easily soluble in Na_2CO_3 solution to yield an orange solution with the characteristic intense purple fluorescence and soluble in sodium hydroxide solution to yield a red solution fluorescing green, The solution in concentrated hydrochloric and sulphuric acids fluoresced green also. Acridone-4-arsonic acid was rather more soluble in dilute hydrochloric acid and in water than its isomer acridone-3-arsonic acid.

3-Methylacridone-2-arsonic acid.

2-Amino-3-methylacridone (1.8 gm.) in concentrated hydrochloric acid (4.5 c.c.) was treated at 0° with sodium nitrite (0.62 gm.) in water (5 c.c.). After standing for half an hour, the deep crimson acid diazo solution was neutralised keeping the temperature at 0°C. with 5N.NaOH solution. To this neutral solution were added 10.5 c.c. of the previously mentioned/

mentioned arsenite solution (cf. acridone-3-arsonic acid) and the whole left to stand overnight. After heating to 30-40° for a short time, the reaction mixture was filtered, and the residue extracted thrice with 5% NaOH solution. The combined red filtrates which fluoresced weakly blue-green, were made acid with dilute hydrochloric acid when an amorphous orange-yellow precipitate of 3-methylacridone-2-arsonic acid was formed. The acid was purified by repeated solution in Na_2CO_3 solution where it showed a weak purple fluorescence, and regeneration with dilute hydrochloric acid. The purified product had no m.p. below 400° C. (Found, As,20.1: $C_{14}H_{12}O_4NAs$ requires As,20.6%).

SUMMARY

I. The Preuss and Binz reaction, i.e. the conversion of o-nitrotoluene to anthranilic acid by concentrated alkali, has been extended to 3-nitro-4-methylphenylarsonic with the formation of 3-amino-4-carboxyphenylarsonic acid.

II. The synthesis of 3-amino, 4-amino-, 3-methyl-4-amino-, 2-amino-3-methyl, 1-methyl-4-amino-, and 7-nitro-3-bromoacridone is described and a review is made of the effect of the nature and position of substituents on the cyclisation of substituted diphenylamine-2-carboxylic acids.

III. The methods of synthesis of acridone arsonic acids are reviewed and examined, and the preparation of acridone-3-, acridone-4-, nitroacridone-3-, and 3-methylacridone-2-arsonic acids described.

The author wishes to thank the Carnegie Trust of the Universities of Scotland for a Research Scholarship, Dr W.O. Kermack for his kind interest and supervision of the work, the Laboratory Committee of the Royal College of Physicians of Edinburgh for granting facilities which enabled the work to be carried out, and Scottish Dyes Ltd., Grangemouth, for a gift of chemicals.